SPECTRUM OF NEUROTUBERCULOSIS AND ANALYSIS OF OUTCOME OF TREATMENT WITH RNTCP DOTS REGIMEN

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CERTIFICATE

This is to certify that this Dissertation entitled, **"SPECTRUM OF NEUROTUBERCULOSIS AND ANALYSIS OF OUTCOME OF TREATMENT WITH RNTCP - DOTS REGIMEN"** is a bonafide record of work done by **Dr.E.UMA MAHESWARI** under our guidance and supervision in the Institute of Neurology, Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai, submitted as partial fulfillment for the requirements of D.M. Degree examination Branch I NEUROLOGY, AUGUST 2013, under the Tamil Nadu Dr. M.G.R. Medical University, Chennai.

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CONTENTS

ABBREVATIONS

RNTCP	-	Revised National Tuberculosis Control Programme
DOTS	-	Directly Observed Therapy Short Course
CSF	-	Cerebrospinal Fluid
ICT	-	Intracranial Tension
TBM	-	Tuberculous Meningites
CT	-	Computerised Tomogram
MRI	-	Magnetic Resonance Imaging
ICA	-	Internal Carotid Artery
OCA	-	Optochiasmatic Arachanoiditis

INTRODUCTION

Tuberculosis is an infectious disease producing a major global health problem worldwide. The incidence rate of tuberculosis in India is very high and accounts for one third of global cases . Annually about 8 million individuals around the world develop TB and 70,000 of these patients acquire TB meningitis . In immune competent individuals, CNS tuberculosis accounts for about 1% of all cases of tuberculosis and 6% of extra pulmonary tuberculosis[1] .

The occurrence of neurotuberculosis goes hand in hand with the incidence of TB infection in the general population . Ten percentage of all patients with tuberculosis have been estimated to have CNS involvement[2]. The various manifestations of neurotuberculosis is included under three major clinical categories: meningitis, tuberculoma brain, spinal tuberculous arachnoiditis.

The Revised National Tuberculosis Control Programme (RNTCP) of Government of India based on universally recommended 'directly observed treatment short-course' (DOTS) therapy was launched in 1997. DOTS therapy in tuberculosis is the standardized treatment of TB patients in India. RNTCP is the largest and the fastest expanding programme in the world .In

India more than 11 million patients have been treated since the inception of the RNTCP [3].

There is no gold standard for the diagnosis of neurotuberculosis unlike pulmonary tuberculosis .This lays an obstacle in diagnosis and management . Very few published data regarding the efficacy of the RNTCP strategy in management of the spectrum of neurotuberculosis exist. Documenting the efficacy of these standardized regimens in the management of neurological TB will be of additional value to the available existing evidence . The present study prospectively assesses the treatment outcomes in patients with various forms of neurological TB who receive the standardized RNTCP treatment regimens.

REVIEW OF LITERATURE.

CNS manifestations of tuberculosis primarily include three clinical categories: meningitis, tuberculoma brain, spinal tuberulous arachnoiditis and the less common clinicopathological entity of TB abscess.

Classification of neurological tuberculosis [4]

Tuberculosis meningitis
Tuberculosis arachnoiditis
Basal
Opticochiasmatic
Spinal
Tuberculoma
Intracranial
Spinal
Tuberculosis abscess

Tuberculosis meningitis

TBM is inflammation of meninges that surrounds the brain due to infection with mycobacterium tuberculosis . It accounts for 70- 80 % of cases

of neurological TB [5,6]. Though it forms the major bulk of neurotuberculosis there is often a delay in the diagnosis and institution of specific therapy for TBM. Early institution of therapy is considered the single most important factor which influences the outcome and development of serious neurological sequelae.

Pathogenesis of CNS tuberculosis

Mycobacterium tuberculosis is the pathogenic organism in causation of tuberculous meningitis by means of haematogenous spread secondary to disease elsewhere in the body. Primary tuberculous infection is associated with bacteremia which will form Rich 's focus in the meninges, parenchyma of the brain or the spinal cord , sub-pial and sub- ependymal surface.. Rich's focus remains silent for many years after the primary infection . Rupture of the lesion results in meningitis ,and growth of the lesion produces tuberculoma[7]. Depending on the number , virulence and immune response of the host, the type and extent of the lesion varies.

The 3 main pathologic features in tuberculous meningitis are: inflammatory meningeal exudates ; vasculitis of the arteries traversing the exudate, mainly small and medium-sized vessels; and disturbance of the flow of the cerebrospinal fluid [8.] These basal exudates are more severe around the circle of Willis [9] . Vessels traversing the exudates are mainly affected .They

produce vessel wall inflammation , narrowing and occlusion of the vessel by thrombus. Tuberculous vasculitis predominantly affect the deep penetrating branches [lenticulostriate, medial striate, thalamo perforating branches] and produce infarcts in the basal ganglia and thalamus[10] . Large vessels like ICA and proximal MCA are also affected .Obstruction to CSF flow at the level of basal cisterns will produce hydrocephalus[11].

CLINICAL FEATURES

Tuberculous meningitis presents itself in 3 stages [11].The clinical manifestation depends on the stage of illness. The early prodromal phase consists of non specific symptoms such as apathy, anorexia, nausea, vomiting, restlessness, behavioral changes which occurs 2- 8 weeks prior to the meningitic phase. The meningitic phase is characterized by headache, vomiting and fever. Neck stiffness is generally not as severe as pyogenic meningitis. In infants, tense fontanelle is a more important sign than neck stiffness. In third stage, raised ICT will dominate the clinical picture and is characterized by altered sensorium, deterioration in vision, pupillary dilatation and pyramidal signs .

Persistent low grade evening rise of temperature is a prominent feature in about 80% of patients. A past history of primary pulmonary tuberculosis is

present in approximately 50% of children with tuberculous meningitis and 10% of adult patients.[12,13,14]

Tuberculous meningitis in addition to causing non specific symptoms also causes Cranial nerve palsies in 20–30% of patients . In patients who ignore the intial vague symptoms the cranial nerve palsy may be the initial presenting manifestation. Among the cranial nerves sixth nerve is most commonly affected. Impairment of vision in TBM may be due to optochiasmatic arachanoiditis , third ventricular compression of optic chiasma (if hydrocephalus develops), optic nerve granuloma, and ethambutol toxicity.

Fundus examination may reveal pappiledema and choroid tubercles . Choroid tubercles as such are very rare , and they are found in patients with TBM associated with military tuberculosis.Only in 10 % of patients such tubercles are found in patients with TBM not associated with military tuberculosis[15].

During the course of the illness patients may develop hemiplegia due to infarction secondary to vasculitis . At times, abnormal movements such as chorea , hemiballism ,generalized tremors, myoclonic jerks and ataxia have been observed in children . Seizures, either focal or generalised, may occur

during acute illness or months after treatment.[15]As the disease progresses, increasing evidence of cerebral dysfunction sets in.Apathy and irritability tend to progress to increasing lethargy, confusion, stupor and coma. The terminal illness is characterised by deep coma, decerebrate or decorticate rigidity, and spasm.

Clinical staging system for tuberculosis meningitis[50 51]

Stage I	:	patient fully conscious and oriented with signs of meningism but no focal signs and no evidence of hydrocephalus;
Stage II	:	patient is confused and/or with focal signs such as squint And hemiparesis; And
Stage III	:	patient having stupor, delirium or coma with complete Hemiplegia or paraplegia.

DIAGNOSIS

Cerebrospinal fluid analysis is pivotal in diagnosing tuberculous meningitis. The abnormalities found in CSF of patients with tuberculous meningitis is a predominant lymphocytic pleocytosis (60–400 white cells per ml) with increased protein levels (0.8–4 g/l) . Polymorphonuclear cells may be observed in the early stages of infection ,which are later replaced by

lymphocytes over the course of several days to weeks . Following initiation of treatment with ATT a paradoxical increase in polymorphonuclear cells or lymphocytes was observed by Sutlas[16].

In elderly immunocompetent patients CSF appears to be normal or acellular. Normal or acellular CSF appears to be more common in the elderly patient (greater than 60 years of age), even in the absence of concomitant HIV infection (Karstaedt et al 1998) . The Opening pressure is usually elevated. Two studies done by Ogawa et al [18] and Leiguarda et al [19]showed that approximately half of both adult and pediatric patients having normal opening pressures.

The CSF sugar values are less than half the serum glucose values. The values may range between 18–45 mg/dl.A negative cytology for malignant cells in the CSF is essential for the diagnosis of TBM. On allowing the **CS**F to stand, a fine clot resembling a pellicle or cobweb may form. The appearance of the faintly visible "spider's web clot" is due to the very high level of protein [20] in the CSF (ie, 1-8 g/L, or 1000-8000 mg/dL).

The gold standard is to document the presence of the tubercle bacilli in the CSF, either by smear examination or by bacterial culture. The yield is high when the ventricular fluid is examined and also by centrifuging the CSF

fluid. The rates of positivity for clinically diagnosed cases range from 25% to 70% and the time duration required for culturing the mycobacterium bacilli is prolonged (several weeks). Due to the inherent difficulties with CSF culture , a number of tests have been developed to establish an early and definitive diagnosis.

Polymerase chain reaction is the best diagnostic technique for diagnosing mycobacterial infection . In Kox et al study the sensitivity of CSF polymerase chain reaction has not exceed 50%[21] . Polymerase chain reaction is becoming increasingly available, and may remain positive 4 or more weeks after the initiation of treatment [22]. Nested polymerase chain reaction which depends on the method for extracting DNA and the amount of DNA in the sample which are crucial in determining the sensitivity [23] . MPB 64 protein encoding gene is most specific for diagnosis of tuberculous meningitis[24] .

Though radioactive bromide partition testing and identification of cell wall components (eg, tuberculostearic acid) were reported to have a sensitivity and specificity over 90%. These test were not of clinical utility. Antibodies against tubercle bacilli can be detected with enzyme-linked immunosorbent assay (ELISA)

The tuberculin test:

A negative tuberculin skin test does not rule out tuberculosis. Tuberculin skin test should not be offered to a patient unless there is a plan to start treatment in event of a positive skin test [25].

IMAGING

Imaging reveals basal enhancement of the meninges (particularly in the perimesencephalic cisterns), hydrocephalus, infarction edema often located periventricularly, and mass lesions due to associated tuberculoma or tuberculous abscess[26] [27] . A study revealed that hydrocephalus was the single most common abnormality seen by CT scan in 52 % to 80% of patients with tuberculous meningitis[28] [29] .The degree of hydrocephalus correlates with the duration of the disease[30] .The next common imaging feature was enhancement of the meninges is seen in approximately 60% of patients with tuberculous meningitis which may be localized or diffuse [31](Goyal et al 1997). Tuberculous pachymeningitis should also be considered in the differential diagnosis of "idiopathic" cranial hypertrophic pachymeningitis(Parney et al 1997)[32]

In children, plain CT showing enhancement in the the basal cisterns has been reported to be a specific sign for tuberculous meningitis (Andronikou 2004)[33].

The third common finding on imaging is infarctions. The majority of infarcts are located in the basal ganglia, internal capsule, thalamus and rare in the large vessel territories.Contrast CT and MRI are superior in demonstratingthe abnormalities than plain CT. Infarction secondary to vasculitis are seen in thalamic, basal ganglion, and internal capsule regions.This occurs due to thrombosis in vessels traversing the perimesencephalic cistern. The basilar exudates are thick and they enhance intensely in the basal cisterns (spider-leg appearance) and in the sylvian fissures. The diffusion weighted images are more sensitive than the conventional MRI , in depicting early ischemic lesions. Two large community based studies analysed the imaging findings in patients with TBM and found that hydrocephalus was found in 78% basal enhancement was found in 38% infarcts in 15-30% and tuberculomas in 5-10% of the patients.

Tuberculomas are nothing but enlarged rich's focus lesions which appear as low- or high-density and rounded or lobulated masses and show intense homogenous or ring enhancement after contrast administration. The distinctive features of tuberculoma are the irregular wall of varying thickness ,

moderate to marked perilesional oedema. The caseating granulomas are distinctive from the non caseating granuloma .Noncaseating granulomas are homogeneously enhancing lesions. Caseating granulomas are rim enhancing; if these have a central calcific focus, they may form a targetlike lesion[34]. Granulomas may also form a miliary pattern with multiple tiny nodules scattered throughout the brain .Tuberculomas are infrequently seen on CT or MRI of patients with tuberculous meningitis. All lesions are surrounded by hypoattenuating edema .Tuberculomas may be single or multiple and are more common in frontal and parietal lobes, usually in parasagittal areas. On CT scanning[35], tuberculomas measure more than 20 mm in diameter, frequently irregular in outline, and are always associated with marked cerebral oedema (leading to midline shift) and progressive focal neurological deficit.The MRI features of tuberculoma depend on whether the lesion is non-caseating, caseating with a solid centre, or caseating with a liquid centre.

The non-caseating granulomas[36] are hypointense on T1-weighted images and hyperintense on T2-weighted images; after contrast administration the lesion usually shows homogenous enhancement.The second type of tuberculomas are hypointense or isointense on T1-weighted images and also on T2-weighted image. After contrast administration there is ring enhancement. These types of granuloma have variable degree of perilesional oedema. The tuberculoma with central liquefaction of the caseous material

appears centrally hypointense on T1- and hyperintense on T2-weighted images with a peripheral hypointense ring which represents the capsule of tuberculoma . Images after contrast administration show ring enhancement.MR spectroscopy with a single-voxel proton technique can be used to characterize tuberculomas and differentiate them from neoplasms. Tuberculomas show elevated lipid peak that are best seen by using the stimulated-echo acquisition mode technique and a short echo time. The carotid or MR angiogram shows changes in vessels of the circle of Willis. These changes include uniform narrowing of large segments, small segmental narrowing, irregular beaded appearance and complete occlusion.

These vascular changes are due to either vasculitis or mechanical compression by the basilar exudate **.**

Chest radiograph

The chest radiographs reveal findings suggestive of pulmonary TB in 25%-50% of adult patients and 50 to 90 per cent of children with TBM seen in western countries

Diagnosis of Neurological TB

The diagnosis of TBM was established as perAhuja et al [37] criteria.

Criteria for the diagnosis of TB meningitis

A. Clinical

(i) fever and headache lasting for more than 14 days (mandatory)

(ii) vomiting, alteration of sensorium or focal deficit (optional)

B. Cerebrospinal fluid

(i) pleocytosis with more than 20 cells, predominantly (greater than 60%) lymphocytes

(ii) protein greater than 100 mg/dL, sugar less than 60% of corresponding blood Sugars

(iii) negative India ink studies and cytology for malignant cells (in relevant situations)

C. Radiological

CT studies of the head showing 2 or more of the following:

(i) exudates in basal cisterns or in Sylvian fissures

(ii) hydrocephalus

(iii) infarcts

(iv) gyral enhancement

D. Evidence of extra-neural tuberculosis

Active tuberculosis of lungs, gastrointestinal tract, urogenital tract, lymph nodes, skeletal system or skin as evidenced by appropriate radiological or microbiological tests or by the presence of caseation necrosis on histopathological examination

The 4 sub-criteria described above have been incorporated into 4 groups in descending order of sensitivity:

1. Definite tuberculosis meningitis: (i) clinical criteria (A); (ii) bacterial isolation from CSF or diagnosis at autopsy

2. Highly probable tuberculosis meningitis

(i) Clinical criteria (A); (ii) All 3 of(B) and (C) and (D); and good response to antituberculosis treatment

3. Probable tuberculosis meningitis

(i) Clinical criteria (A); (ii) Any 2 of B, C and D

4. *Possible tuberculosis meningitis*

(i) Clinical criteria (A); (ii) Any one of (B) (C) and (D)

INTRACRANIAL TUBERCULOMAS

Definition

Tuberculoma is a mass of granulation tissue made up of a conglomeration of microscopic small tubercles**.** Macroscopically a typical tuberculoma is a well defined grayish avascular mass with a yellow caseating core. Histologically the central necrotic core is surrounded bytuberculous granulation tissue containing epitheliod cells , lymphocytes and langhans giant cells. Surrounding the tuberculoma there may be arterites,

neuronal damage and edema of varying degree of severity . As the tuberculoma regresses there is increasing collagen formation , sometimes associated with deposition of calcium salts.Tubercle bacilli can be found in majority of surgical specimens or autopsy specimens, but in their absence the pathological diagnosis can made on the histological appearance of the granuloma alone[41]. In most cases lesions are solitary but in 15- 34 % of cases multiple tuberculoma are found[42].

CLINICAL FEATURES

Most often patients present with signs and symptoms of space occupying lesions . Compared with other space occupying lesions the incidence of convulsions is high as much as 85%[43] . Fever and ill health are unusual findings , but a past history of tuberculosis or a evidence of active tuberculosis outside the CNS occurs in about 50% of the patients[41]. 60- 70% of intracranial tuberculoma present with seizures. 56 – 93 % have features of raised intracranial pressure. 33- 68% have focal neurological defecit. Gulati et al found the commonest cause of focal seizures is tuberculoma[42].A single confluent large granuloma with necrotic centre63 – 73 % of patients. Tuberculomas may also be multiple.

In the early phase of the illness edema, necrosis may appear as low attenuating areas on CT scan. Once the granuloma starts to organize there

may be high attenution , contrast enhancement and calcification as well as ring enhancement with variable degree of surrounding edema.

Criteria for the diagnosis of tuberculoma

Clinical

(i) the presence of clinical evidence of raised intracranial pressure (ICP) with headache and vomiting and/or papilloedema

(ii) the presence of progressive focal neurological deficit (motor or sensory)

CT features

(i) the size of the lesion (largest dimension) > 20 mm

(ii) irregular shape of the lesion

(iii) the presence or absence of a midline shift as evidenced by the shift of any one of the midline structures, namely the interhemispheric fissure, septum pellucidum, or the third ventricle

Response to antituberculosis treatment

(i) Good clinical and radiological response to antituberculosis treatment

TUBERCULOSIS RADICULOMYELITIS (TBRM)

Tuberculosis radiculomyelitis is a form of spinal TB and may develop in one of the three ways: [i] as a primary TB lesion; [ii] TBM extending downwards [iii] an extension from vertebral TB . TBRM includes cases

designated as arachnoiditis, intradural spinal tuberculoma or granuloma and spinal cord complications of TBM.

Treatment

Antituberculosis treatment is the main stay for the treatment of neurological TB.The absence of a gold standard diagnostic test is the main hurdle in the management of neurotuberculosis. There should neither be a delay or nor injudicious usage of ATT as it is potentially toxic and is required for a long period. Diagnosis by either by PCR or by immunological methods is seldom possible in every case, because of the limited facilities. A CSF study is mandatory if there is no contraindication for a lumbar puncture. If suspicion of TBM is high then anti tuberculosis treatment should be initiated at the earliest. The pros and cons of initiating anti tuberculosis treatment before the confirmation of the diagnosis should be carefully weighed in each patient. However, the most important principle of therapy is that anti tuberculosis treatment should be initiated when the disease is suspected. It should not be delayed until proof of diagnosis of TBM has been obtained.

Treatment regimens

There are no convincing randomized, controlled clinical trials to suggest that any particular regimen is superior in the treatment of TBM. The recommended drugs are isoniazid, rifampicin, pyrazinamide and ethambutol

or streptomycin. Ethambutol is preferred over streptomycin because of its better CSF penetration. The British Infection Society recommends 4 drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) for 2 months followed by 2 drugs (isoniazid and rifampicin) for at least 10 months[45] for all forms ofneurotuberculosis. The drugs exhibit differences in CNS penetration Isoniazid, pyrazinamide, and ethionamide penetrate readily into cerebrospinal fluid, whereas rifampin, ethambutol, and streptomycin do so poorly, especially in noninflamed meninges.[46] Penetration through inflamed meninges is excellent, with CSF concentration 90% that of serum; however, in the absence of inflammation the penetration is about 20% of serum levels . Drug toxicity with isoniazid includes hepatotoxicity, peripheral neuropathy when pyridoxine is not co-administered, seizures, alterations in mental state, and potentiates phenytoin toxicity. Rifampin, a bactericidal against intracellular and extracellular bacilli, achieves high serum levels after oral administration. Cerebrospinal fluid levels are approximately 20%, or less, of serum levels in the presence of meningeal inflammation. Pyrazinamide has its bacteriostatic effect on intracellular rather than extracellular organisms and penetrates the CSF well. Some have shown cerebrospinal concentrations of 100% of the serum concentration.In the presence of meningeal inflammation ethambutol achieves CSF concentrations of 10% to 50% of serum levels. The chief toxicity of this tuberculostatic drug is retrobulbar neuritis, which develops in as many as 1% of persons on the currently recommended dose.

Careful attention to visual acuity and color perception is required while the patient is on this drug. Streptomycin penetration into cerebrospinal fluid requires meningeal inflammation for levels to approximate one quarter of that of the serum . Streptomycin must be given parenterally, and renal failure and ototoxicity are its chief adverse effects.

ROLE OF STEROIDS IN TUBERCULOUS MENINGITES:

Steroids reduce the inflammation and the neurological complications ,thus enhancing Recovery[38].Adjunctive glucocorticoid therapy is beneficial in both adults and children with tuberculous meningitis[39].The benefit was most evident for patients with early disease. The adverse reactions due to usage of steroids include gastrointestinal bleeding, infections hyperglycaemia, osteoporosis and neutropenia .Glucocorticoid regimen[40] followed is either dexamethasone or prednisone. Dexamethasone is used with a total dose of 8 mg/day for children weighing <25 kg; 12 mg/day for adults and children >25 kg, for 3 weeks, then tapered off gradually over the following 3 to 4 weeks.Prednisone is used with a dose of 2 to 4 mg/kg per day for children; 60 mg/day for adults, for 3 weeks, then tapered off gradually over the following 3 weeks.

Surgical intervention is required in the management of obstructive hydrocephalus, although in the absence of obstruction hydrocephalus may be

managed medically. When reducing elevated intracranial pressure in the latter instance, the use of furosemide and acetazolamide was significantly more effective than antituberculous drugs alone[47]. Although a ventricular drain is helpful in the acute stages, ventriculoperitoneal and ventriculoatrial shunts are effective and should not be delayed until the infection is eradicated. Surgery may also be necessary in the face of tuberculomas or tuberculous abscesses developing in tandem with tuberculous meningitis. However, tuberculomas often resolve with adequate therapy, and unless there is impending cerebral herniation or compromise of the anterior visual pathways, the procedure may prove unnecessary.

Surgery is also mandated when the diagnosis of a CNS tuberculoma is in doubt. Some investigators recommend medical trials of antituberculous medication for a duration of at least 2 months before resorting to surgical exploration in suspected cases [48]. Paradoxical progression of CNS tuberculosis with the appearance of new lesions on radiographic imaging may occur immediately after the institution of appropriate treatment [49]. Similarly, 2 to 18 months after the initiation of adequate antituberculous therapy, enlarging intracranial tuberculomas may result in clinical deterioration. Teoh and Humphries found that the organisms isolated from these enlarging tuberculomas were sensitive to the antibiotic employed and suggested that their appearance was an immunological phenomenon[50]. Surgery can usually

be avoided with the administration of corticosteroids and continued antituberculous therapy. Resolution of the fever may require weeks. CSF glucose levels return to normal within 2 months in 50% of patients and within 6 months in almost all, whereas the CSF pleocytosis requires more than 6 months to resolve in 25% and the CSF protein remains elevated in 40% at this time [51]. Additionally, the continued alteration in level of consciousness in the early stages of the disease may be the result of concomitant hydrocephalus or hyponatremia.

A study of tuberculous meningitis in inner-city Atlanta revealed a mortality rate of 41.2% despite the initiation of appropriate therapy within 3 days of hospital admission. . A large study from Vietnam reported that survival of tuberculous meningitis is substantially worse in the HIV-infected population (Thwaites et al 2005). Whereas the clinical manifestations were not different between the HIV-infected and non-infected groups, mortality at 9 months was 64.6% in the former and 28.2% in the latter[45](Thwaites et al 2005). The sequelae include cognitive disturbances, seizures, hemiparesis, ataxia, visual impairment accompanying optic atrophy, and other persistent cranial nerve palsies [53, 54]

AIMS AND OBJECTIVES

1) To study the clinical spectrum of neurotuberculosis.
2) To prospectively study the treatment outcomes in patients with various forms of neurotuberculosis being treated with the standardized RNTCP DOTS regimen.

MATERIALS AND METHODS

Patients diagnosed to have neurotuberculosis in Rajiv Ghandhi Govt. General Hospital during the period January 2012 to December 2012 were prospectively studied . Patients were enrolled from Neurological services from RGGGH .

Diagnosis of Neurological TB

The diagnosis of TBM and tuberculoma was done as per the Ahuja et al [37]criteria and Rajasekhar et al[35] respectively . Patients with "definitive" and "highly probable" TB meningitis as per the criteria were included in the study .

Inclusion Criteria

New cases of TBM, tuberculoma with or without spinal arachnoiditis whose CSF analysis were negative for fungal infection, malignant cells were enrolled.

Exclusion Criteria

1) Patients with known serious cardiac disease, renal failure, liver disease, hematological abnormalities , chronic alcoholism were excluded from the study.

2) Presence of secondary immunodeficiency states, such as HIV infection, AIDS organ transplantation, malignancy, etc.,
3) Currently receiving cytotoxic therapy, or have received it within the last 3 months
4) Pregnancy and lactation
5) Hypersensitivity to antituberculosis drugs

Ethical clearance

The study was cleared by Institutional Ethical Committee (vide letter Roc.No.39092011).

Clinical evaluation and investigations

Informed consent was obtained from all the patients for participation in the study. In all of them, a detailed history was taken and a thorough physical examination was done.

The neurological status was ascertained on admission , level of sensorium, meningeal signs, focal deficits in the form cranial nerve palsy, hemiparesis and evidence for raised intracranial pressure was evaluated. Clinical staging of the illness was done after clinical evaluation . Base line investigations was done to rule out hematological abnormalities, renal and hepatic functions.

Lumbar puncture was performed and the CSF total count, lymphocyte count,typical cells, protein and sugar levels were estimated at the time of initial evaluation.CSF was sent for AFB and grams staining . All the CSF samples were also sent for fungal staining . Repeat CSF examination was carried out when clinically indicated.

At the time of initial evaluation, plain and contrast-enhanced CT of the brain was done in all patients with neurological TB ; plain and gadolinium enhanced MRI of the brain was done if the clinical situation warrants . During the follow-up visits, imaging investigations and other appropriate investigations were repeated when clinically indicated.

Treatment and follow-up

All patients with neurological TB were categorized as per the RNTCP guidelines . New patients with neurological TB treated under Category I, received $2(H_3R_3E_3Z_3)/7(H_3R_3)$ (total duration nine months). The continuation phase of treatment was further extended in selected patients as per the need. The continuation phase of treatment was further extended in selected patients as per the need under DOTS cat.I . In patients with TBM, initially, intravenous dexamethasone was administered according to the body weight as follows: under 25 kg 8 mg/day; above 25 kg 12 mg/day for 1 to 2 weeks. This was followed by oral prednisolone in a dosage of 1 to 2 mg/day for children

and 60 mg/day for adults for 2 to 3 weeks. Thereafter, the oral prednisolone was gradually tapered off over the next 2 to 3 weeks and then stopped.

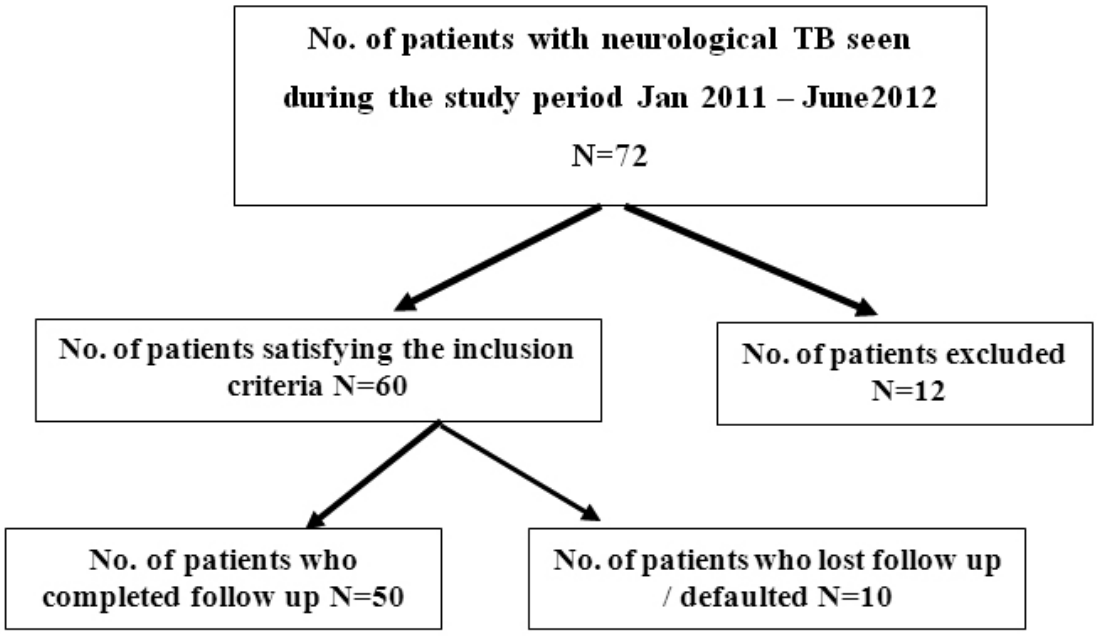
In patients with brain tuberculomas , oral prednisolone was administered in a dosage of 1 to 2 mg/day for children and 60 mg/day for adults for 3 weeks. Thereafter, the oral prednisolone was gradually tapered over the next 3 weeks and then stopped.The patients were followed-up on a monthly basis till they completed the end

Outcome

The treatment outcomes were defined as per the RNTCP guidelines as "treatment success" (defined as a patient who has either been cured or has completed treatment) and "default" (patients whose treatment was interrupted for 2 consecutive months or more). New cases who manifested clinical, radiological and/or bacteriological deterioration in spite of 5 months of adequate treatment were termed as "treatment failure".

RESULTS

Seventy two patients diagnosed to have neurotuberculosis between Jan. 2012 and dec 2012 were evaluated . Of the 72 patients, 60 patients who satisfied the inclusion criteria were recruited for the study after obtaining consent and they were followed up. Twelve patients were excluded from study due other associated comorbidities like cardiac illness, renal, hepatic illness , immunocompromised state and haemotological abnormalities.

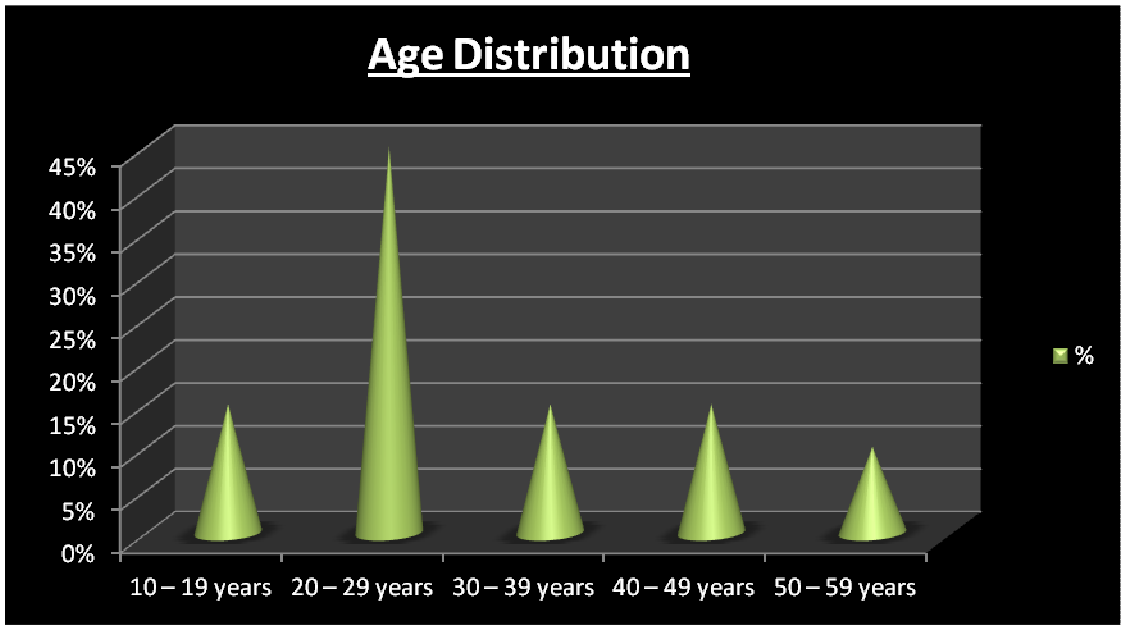


1) AGE DISTRIBUTION:

The age distribution of patients enrolled in the study is shown in Table 1. The age group of the enrolled patients were in the range of 14 to 59. The mean age was 28yrs. Majority of the patients were in the age group 20-29 years (45%).

Table:1

Age Group	No. (n=60)	%
10 – 19 years	9	15%
20 – 29 years	27	45%
30 – 39 years	9	15%
40 – 49 years	9	15%
50 – 59 years	6	10%

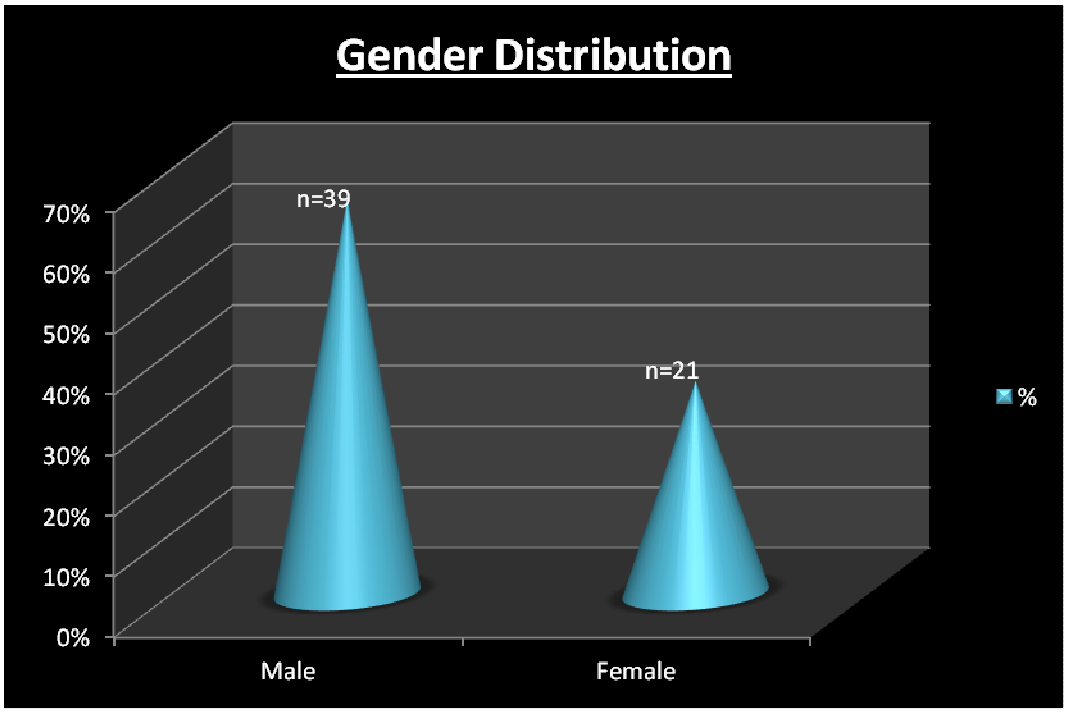


2) GENDER DISTRIBUTION:

Overall Neuro tuberculosis has male preponderance with a ratio of Male/Female 65:35.

Table 2 :

Sex	n=60	%
Male	39	65%
Female	21	35%



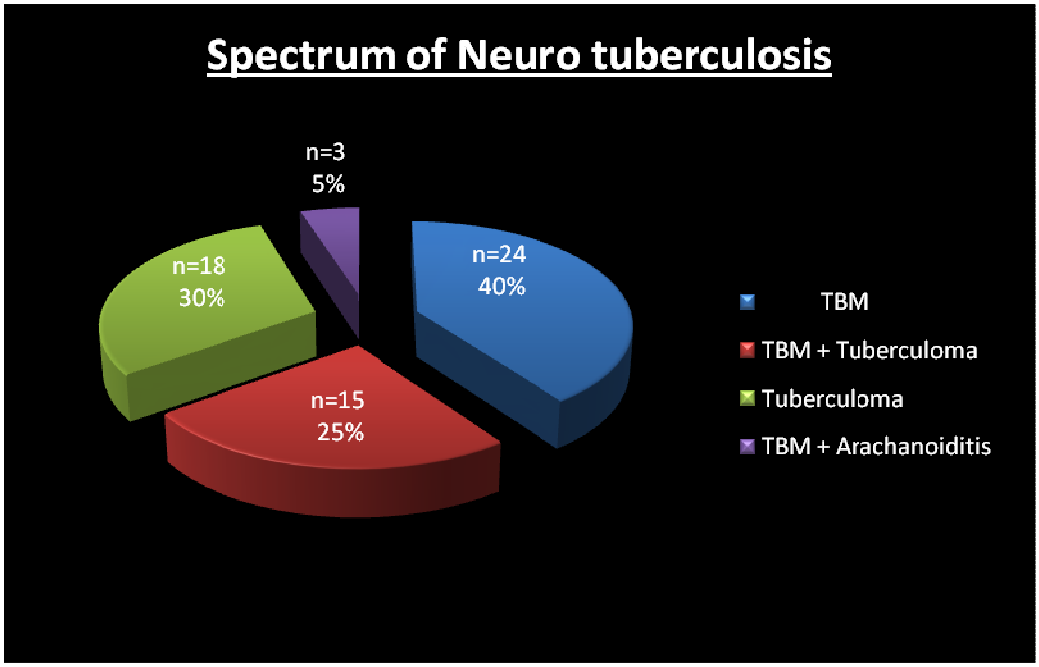
3) SPECTRUM OF NEURO-TUBERCULOSIS

The various forms of presentation of neurotuberculosis is shown below in the table 3.

Table 3 :

Spectrum of Neuro tuberculosis	N=60
TBM	**24**
TBM + Tuberculoma	**15**
Tuberculoma	**18**
TBM + Arachanoiditis	**3**

Various forms of Neuro TB:



4) CLINICAL FEATURES :

a) Tuberculous Meningites (N= 24) :

Of the varied manifestations of neurotuberculosis , tuberculous meningitis (40%) ranks first . The common symptoms on presentation in patients with TBM in our study were head ache, and fever which are the mandatory symptoms for diagnosis of TBM according to Ahuja et al criteria [37]. The common signs included altered sensorium, seizures, focal deficits in the form of haemiparesis, and cranial nerve palsy are depicted below in table 4.

Table 4:

TBM	n=24	%
Headache	24	100%
Fever	24	100%
Altered Sensorium	20	83.3%
Focal Deficits	18	75%
Seizures	12	50%
Vision impairment	4	16.66%

b) Tuberculomas (N=18) :

Tuberculomas (30%) ranks second next to TBM among the spectrum of illness. The common presenting signs and symptoms of tuberculoma were seizures followed by head ache , fever and focal deficits. They are depicted below in table 5

Table 5 :

Tuberculoma	**n=18**	**%**
Seizures	18	100%
Headache	9	50%
Fever	15	83%
Focal Deficits	2	11.11%
Choreoathetoid movement	1	5.55%

c) TBM & Tuberculoma : (n=15)

The common presentation in patients with TBM and tuberculoma are head ache, fever , altered sensorium, seizures and focal deficit.

Table : 6

Variable	**n=15**	**%**
Headache	15	100%
Fever	12	60%
Altered Sensorium	8	53.33%
Seizures	10	66.6%
Focal Deficit	6	40%
Vision impairment	2	13.33%

d) Spinal Arachanoiditis (N= 3) :

Three cases of TBM with spinal arachanoiditis were enrolled . The clinical manifestations of the patients were fever, headache, and seizures. Physical examination revealed neck stiffness, optic atrophy, bilateral VI cranial nerve palsy and paraplegia.

5) MRC CLINICAL STAGING OF ILLNESS :

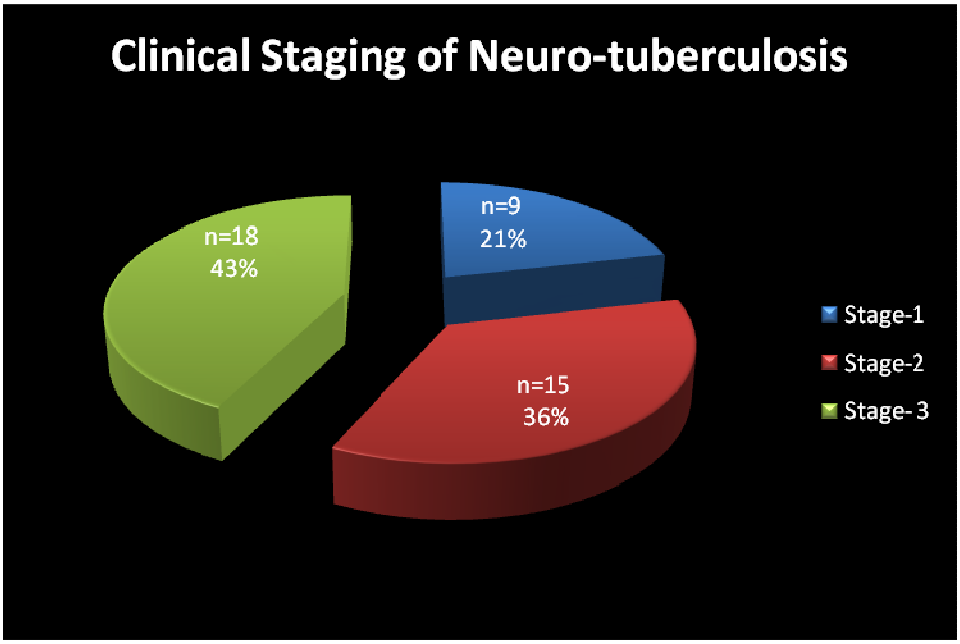
Stage 1	Fully Conscious, no paresis
Stage 2	Decreased level of consciousness, no paresis
Stage 3	Deeply comatose with or without dense neurological deficit

a)TBM (with or without tuberculomas / spinal arachonoiditis)

The patients with TBM were staged according to MRC staging The clinical staging on admission in 42 patients is as follows.

Table 7 :

Stages	n=42	%
Stage-1	9	21.4%
Stage-2	15	35.71%
Stage- 3	18	42.85%



6) INVESTIGATIONS :

a) Cerebrospinal fluid analysis findings :

The CSF examination findings in 42 patients with TB meningitis are shown in Table 8. In none of the patients we were able to document AFB in the CSF .

CSF findings in patient with TBM (with or without tuberculomas / spinal arachonoiditis)

Table 8:

Varibles	Stage 1 (n=9)	Stage 2 (n=15)	Stage 3 (n=18)	Percentage (n=42)
1) Proteins mg/dl				
<100	7	5	2	33.3%
101- 500	2	8	6	38%
> 501	-	2	10	28.5%
2) Cells				
<20 (lymphocyte predominant)	3-	2	5	4.7%
>20 (lymphocyte predominant)	3	4	4	38%
>100 (lymphocyte predominant)	3	9	9	57%
3) Sugar				
Normal	7	7	10	57%
< 2/3rds serum levels	2	8	8	42%
4) AFB stain	Negative	Negative	Negative	-
5) Fungal stain	Negative	Negative	Negative	-

b) IMAGING

The most common imaging findings in patients with isolated TBM was, meningeal enhancement (83.33%) followed by hydrocephalus (66.66%), basal exudates (37.5%) and infarcts (16.6%). In patients with TBM with

tuberculoma the most common abnormality was meningeal enhancement (53.33%) followed by basal enhancement (40%), hydrocephalus in (20%) and infarcts in (20%).In patients with TBM and spinl arachanoiditis all the three patients had hydrocephalus, meningeal enhancement and basal exudates

Imaging findings in patient with TBM

Variable	TBM (n=24)	TBM + Tuberculoma (n=15)	TBM + Spinal arachnoiditis (n=3)	All patients (n=42)
Infarct	4 (16.66 %)	3 (20 %)	-	7(16.66%))
Hydrocephalus	16 (66.66%)	3 (20%)	3(100)	22(52 .3%)
Meningeal enhancement	20 (83.33%)	8(53.33%)	3(100)	31 (73.80%)
Basal exudates	9 (37.5%)	6 (40 %)	3(100)	18(42.85%)
Granuloma	-	15 (100 %)	-	15 (35.7%)

Brain Tuberculomas : (n=18)

Table 9

	solitary	Multiple
Tuberculoma (N= 18)	12	6
TBM /TuberculomaStage (N=15)	3	12

Table 10

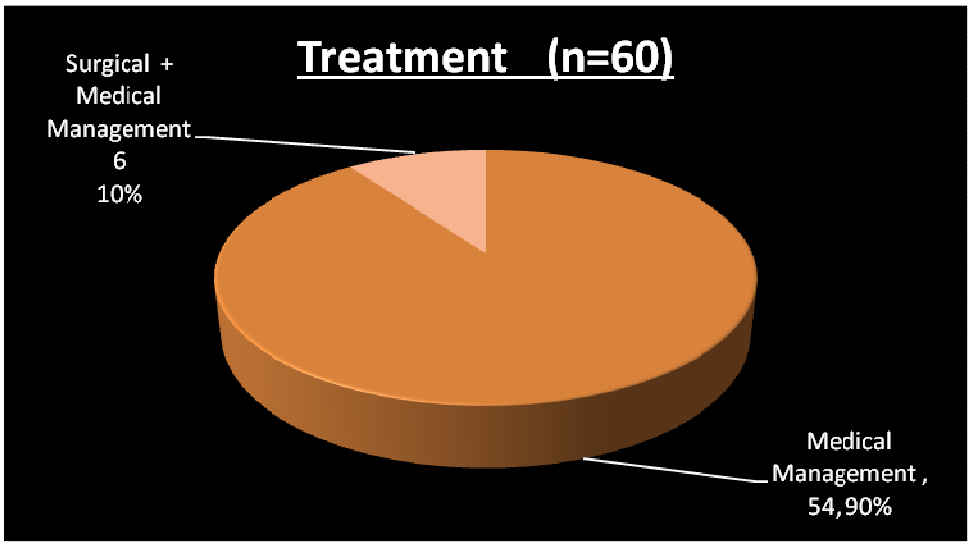
Location	Site	N
Supratentorial	Parietal	9
	Temporal	2
	Frontal	6
	Occipital	-
Infratentorial	Brain Stem	1
	Cerebral	-
	Spinal Cord	-

Among 18 cases of tuberculomas 12 cases had solitary lesions and 6 cases had multiple lesions. In patients who presented with TBM and tuberculoma (n= 15) multiple tuberculoma was seen in 12 cases and solitary lesions in 3 cases.

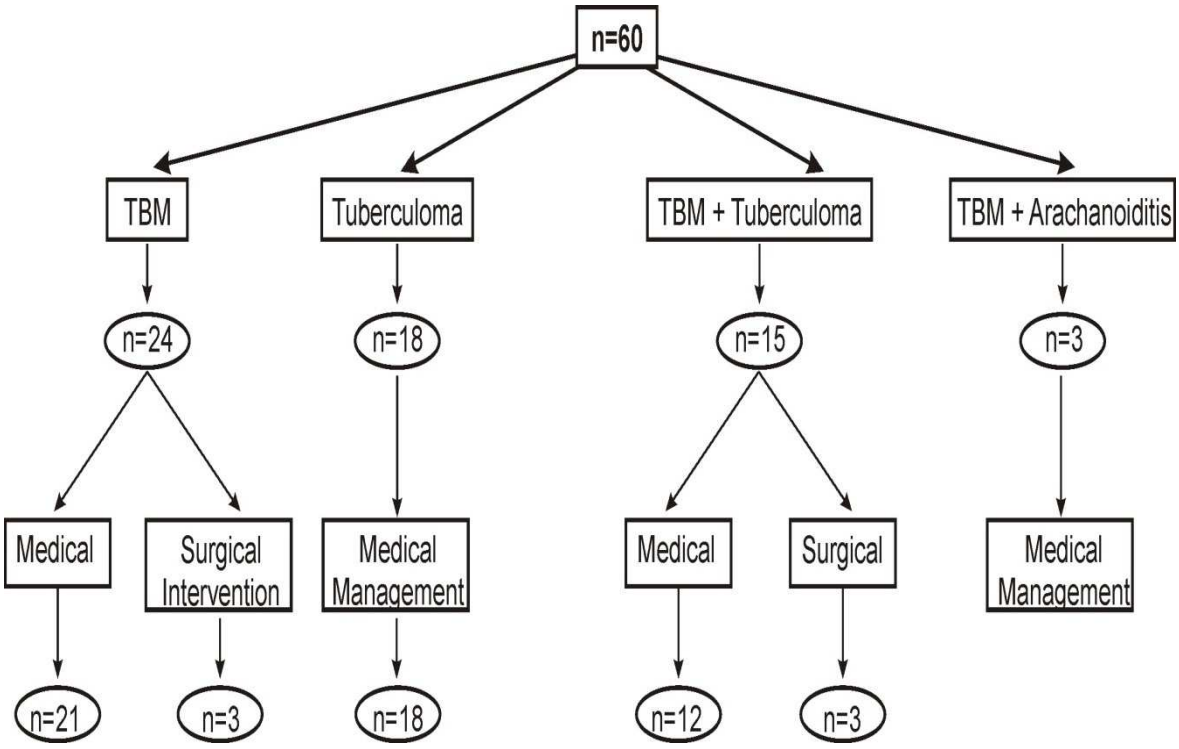
7) TREATMENT n=60 :

a) Medical Management n=54 (90%)

b) Surgical + Medical Management n=6 (10%)



ENTIRE SPECTRUM OF NEUROTUBERCULOSIS WITH THE MODALITY OF MANGEMENT



All the 60 patients enrolled in this study were new cases of tuberculosis and hence entitled to receive Cat.I ATT and steroids according to the prescribed protocol.

CAT.I ATT

Seriously ill	IP	- 2 H_3 R_3 Z_3 E_3
Extra pulmonary	MP	- (7-10) H_3 R_3

Table 11

Type of Surgical Intervention	n=6
VP Shunt	5
Drainage of abscess	1

8) FOLLOW-UP

Follow-up of these patients were made monthly and they were evaluated for clinical, radiological and bacteriological / CSF analysis for subsequent improvement / deterioration during the follow-up.

Treatment was initiated in all the 60 patients of neurotuberculosis with Cat. I ATT, and steroids (i.v decadron) in the dose of 0.4 mg per Kg body weight for 1 week 0.3 mg/Kg body weight in second week, 0.2 mg/kg body weight in the third week , 0.1 mg/kg body weight in the fourth week . At the end of 4 weeks patients were switched over to oral prednisolone at the dose of 1 mg/kg body weight and the dose gradually tapered and stopped in 4 weeks.

Among the 60 patients followed up 6 patients lost follow up (4 cases of TBM +/- Tuberculoma +/- Arachnoiditis and 2 cases of isolated

tuberculoma) and four cases defaulted drugs. (2 cases of TBM and 2 cases of tuberculoma).

Among the 50 patient who were regularly followed up, 6 patients level of sensorium worsened (2 patients progressively worsened since admission) . Subsequent imaging in these patients showed worsening of the grade of hydrocephalus requiring VP shunt in 5 patients . On subsequent follow up these patients developed shunt dysfunction, shunt infection, increase in the size of the tuberculomas and 2 patients out of 5 succumbed to death in the 3 rd month of treatment. In addition these patients required anti edema measures. Two patients showed improvement and they required 12 months of ATT and they finally completed treatment successfully. In one patient there was tuberculous abscess formation and drainage of the abscess was done through a frontal burr hole. Later this patient developed bilateral hemorrhagic infarct due cerebral venous sinus thrombosis at 7th month of ATT, communicating hydrocephalus with features of raised intracranial pressure . Finally this patient was considered to be a treatment failure case in view of occurrence clinical and radiological worsening after 7 months of ATT.

In 18 cases of tuberculoma , 12 were solitary lesions and a minimal regression of the lesions were noted . In 6 cases with multiple lesions 2 cases defaulted treatment , 2 cases lost follow up and in the remaining 2 patients there was an worsening of symptoms with increasing frequency of seizures

and imaging showed increase in the size of lesions and occurrence of new lesions. These case were given 12 months of ATT. These cases were labeled as treatment failure .

Adverse drug reactions

Two patients (3.3%) in our study developed antituberculosis drug-induced hepatotoxicity. The first-line drugs were stopped and the patient was treated with streptomycin, and ethambutol till the liver functions normalized. The first-line drugs could be successfully reintroduced in both the patients .

9) DURATION OF TREATMENT WITH ATT :

a) TBM (with or without tuberculomas / spinal arachonoiditis) : N= 42

Table 12:

Duration Of ATT	Stage 1 (n=9)	Stage 2 (n=15)	Stage3 (n=18)
9 Months	9	12	-
10 Months	-	-	-
12 Months	-	-	13

10)COMPLICATIONS

Table :13

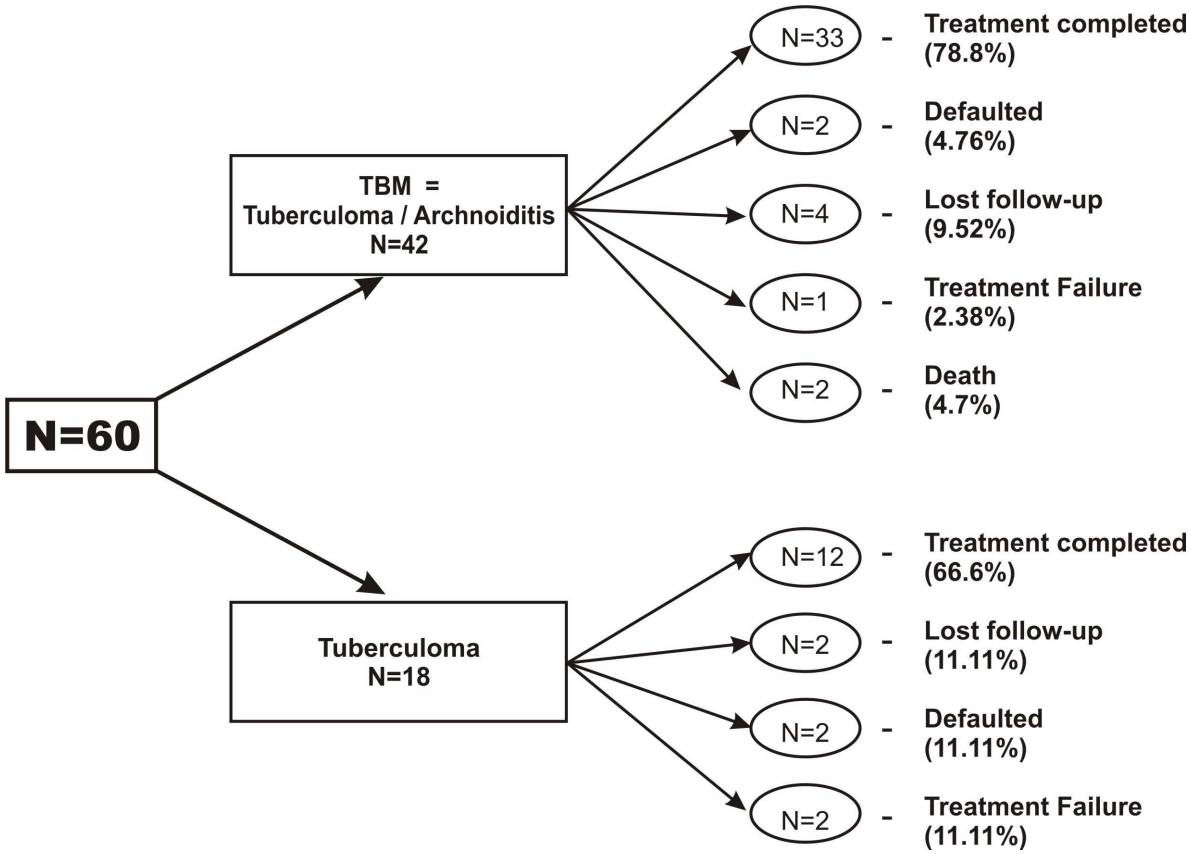
Variables	Stage 1 n=9	Stage 2 n=15	Stage 3 n=18	Percentage
Focal deficit	-	12	18	71.42%
Hydrocephalus	-	7	15	52.38%
Tuberculomas (new lesions/ enlargement of existing lesions)		2	5	16.66%
Tuberculous abscess	-		1	2.38%
Opticochiasmatic Arachanoiditis	-	2	6	20%
SIADH		3		7.14%
Vascular infarcts	-	3	4	16.66%
Spinal Arachanoiditis	-	3	-	7.14%

Patients who presented with isolated tuberculomas (n= 18) 12 had solitary and 6 had multiple lesions. Among the 14 patients who completed follow up showed 2 devoloped new lesions , and there was increase in the size of the preexisting lesions in 2 patients , the outcome of treatment in these two patients was treatment failure .In the remainng 12 patients radiological resolution was observed in only 6 patients.

11) DEFINITIONS OF OUTCOMES

Outcomes	Definition
Treatment Success	Defined as a patient who has been entirely cured or has completely healed.
Default	Patients whose treatment was interrupted for 2 consecutive months.
Treatment Failure	New cases who manifest clinical, radiological and bacteriological deterioration inspite of 5 months of adequate treatment.

12) TREATMENT OUTCOME



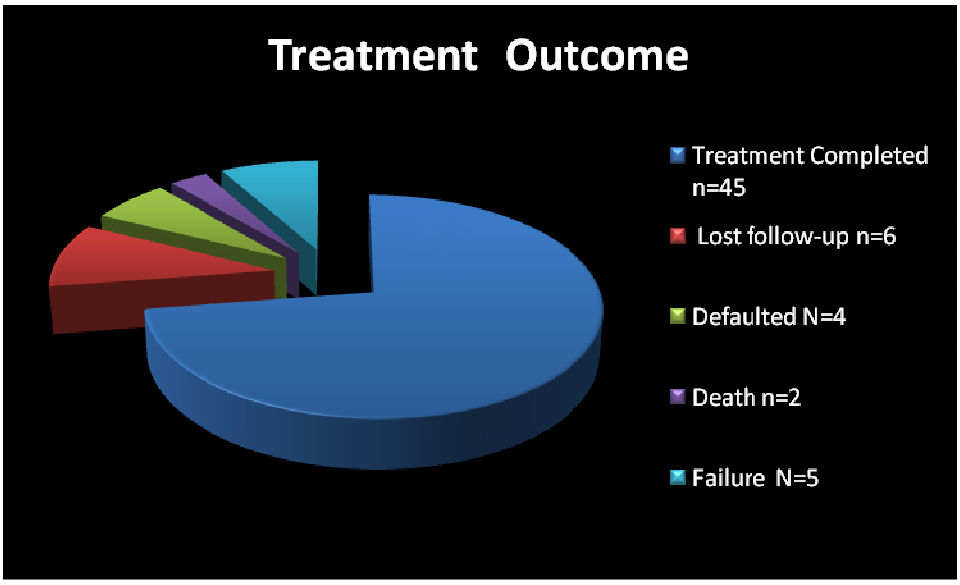
a) Treatment outcome in 42 patients with TBM (with or without brain and spinal tuberculomas; spinal arachnoiditis) and 18 patients with brain tuberculomas

Treatment outcome	TBM (n=42) No. (%)	Brain tuberculomas (n=18) No. (%)
Successful outcome (completed treatment)	33 (78.8%)	12 (66.66%)
Treatment failure	01 (2.38%)	02 (11.11%)
Defaulters	02 (4.76%)	02 (11.11%)
Death	02 (4.76%)	00 (0)
Lost to follow-up	04 (9.52%))	02 (11.11%)

b) Analysis of the outcome in the entire spectrum of neurotuberculosis

Table 14

Total	n=60	%
Treatment Completed	n=45	75%
Lost follow-up	n=6	10%
Defaulted	N=4	6.66%
Death	n=2	3.3%
Failure	N=5	8.33%



13) Correlation of Treatment Outcomes With Clinical Stage In Tbm

(with or without brain tuberculoma and spinal archanoiditis):

Table 15

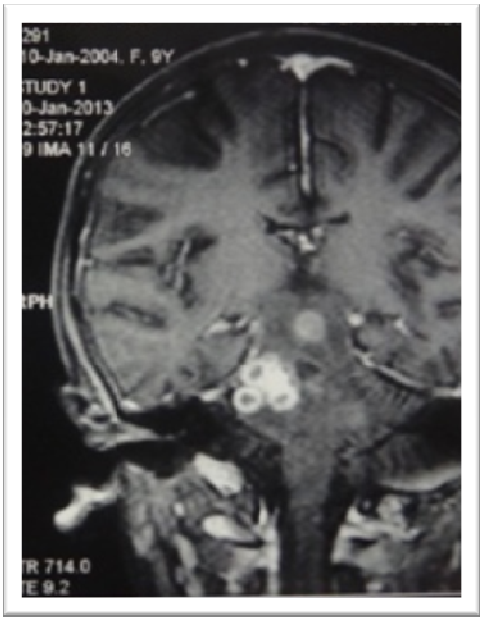
Variable	Total n=42	Stage 1 (n=9)	Stage 2 (n=15)	Stage3 (n=18)
Treatment Completed	33	9	12	12
Lost follow-up	4	-	3	1
Defaulted	2		-	2
Death	2	-	-	2
Failure	1	-		1

Brain Stem Tuberculomas showing minimal change in the size of the lesion after completion of 9 months of

ATT – RNTCP CAT 1 DRUGS

FIG 1

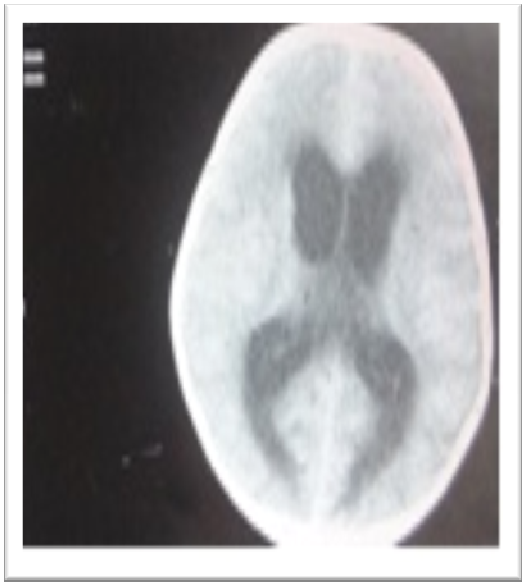
FIG 2



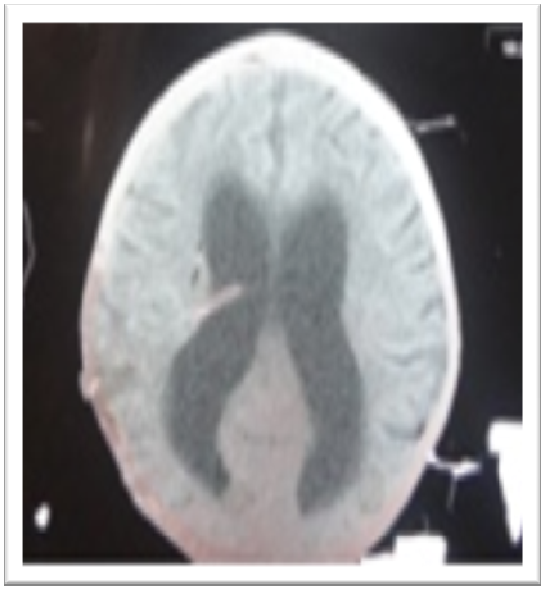
Sequential Images In a girl Who Presented With TBM And Hydrocephalus

Underwent VP Shunt And Subsequent Shunt Related Complications

1) Hydrocephalus

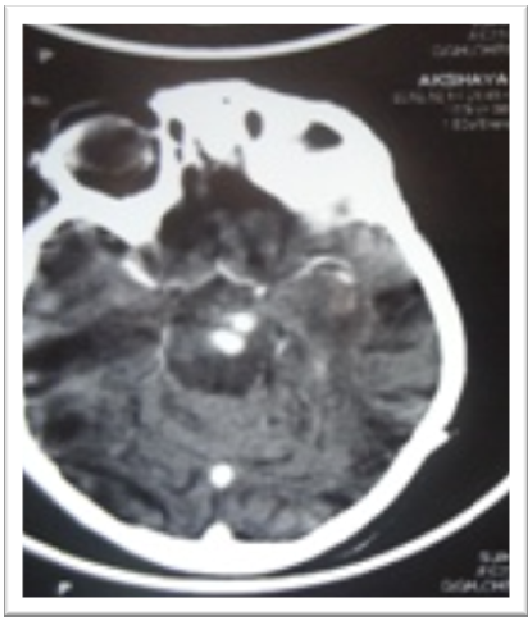


2) Right VP Shunt



3) Shunt Revision

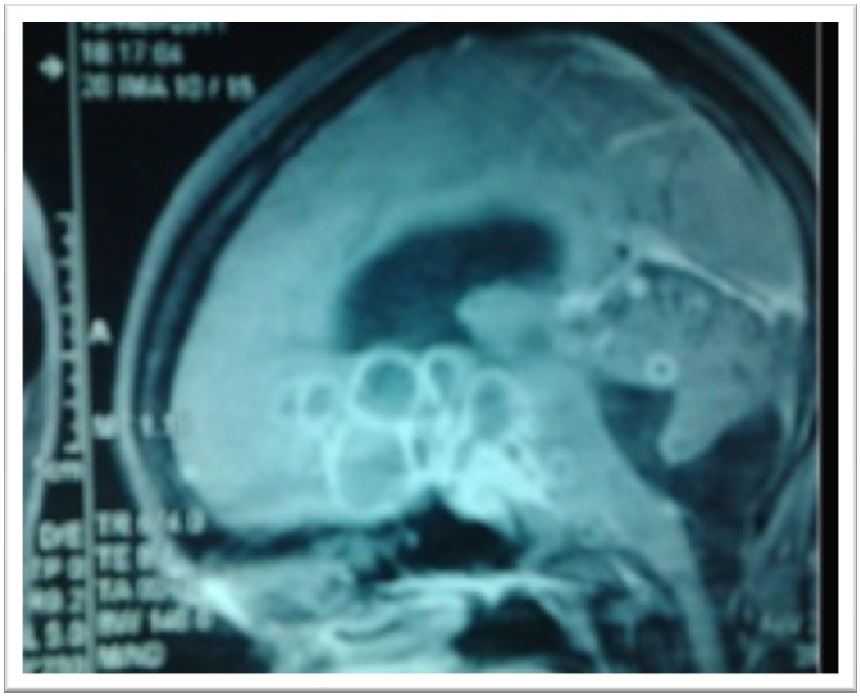
4) New Lesions



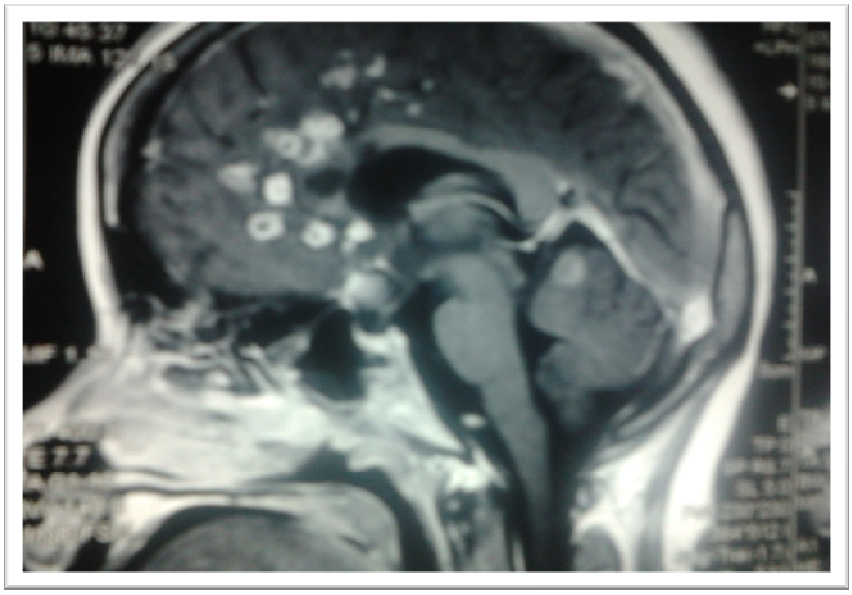
Multiple Conglomerulte Lesions With Meningeal Enhancement

a) Coronal view

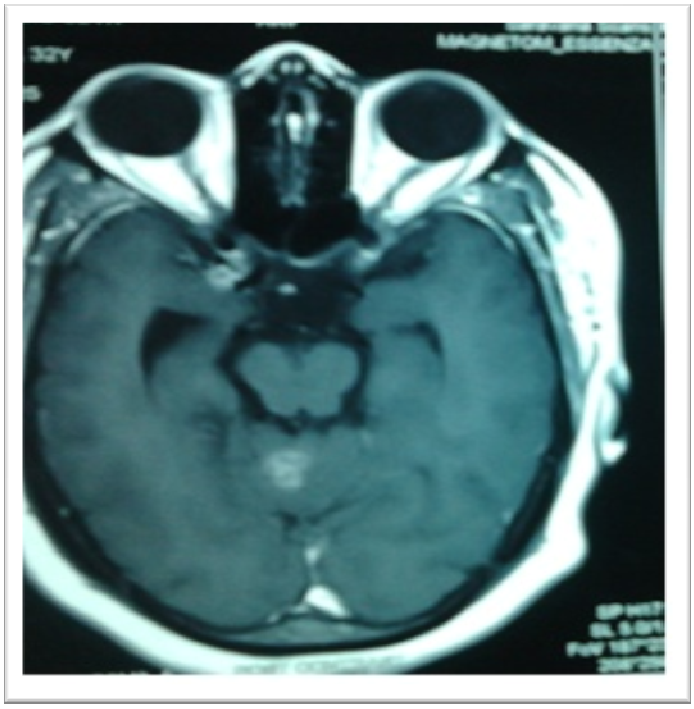
b) Saggital view



Reduction In The Size Of The Lesions And Occurrence Of New Lesions After 9 Months Of Treatment



Contrast enhancement seen in the optochiasmatic region



DISCUSSION

The incidence of tuberculous infection in India is very high contributing to one fifths of the global burden of tuberculosis. Our institute is is tertiary care centre catering to the health needs of the Chennai and Southern India . We have a RNTCP unit functioning in our hospital . Cases were diagnosed based on clinical examination and available investigationas. Highly propable cases of neurotuberculosis were registered under DOTS and drugs were issued and the patients were subsequently followed up at monthly intervals.

Demographic Factors

Sixty patients of new cases of neurotuberculosis were registered and followed up prospectively. The demographic profile of the patients registered was that the affected were in the age group of 10 to 59 patients. Majority of the affected were in the age group 20- 29.There is a male predominance in the distribution of the illness, whereas WHO reports a equal distribution among males and females. the sex distribution males are more affected than the females.

Clinical Manifestations

The clinical manifestation of our patients were protean . Patients diagnosed as highly propable cases of tuberculous meningit(according to

Ahula et [37] criteria) all had the mandatory clinical features of fever and head ache of more than 2 weeks duration . This is consistent with the study done by Thwaites et al [48] . Patients were reffered to us with a prolonged duration of fever ranging from 2 weeks to 3 months being treated by the primary care physicians after evaluation for causes of fever. Majority of these patients did not have a system localization at the beginning of the fever and on investigating were found to be positive for widal and leptospirosis and was treated accordingly. The occurrence of vague symptoms and lack of significant signs and symptoms pertaining to nervous system leads to the fallacy in the diagnosis. Patients on arriving at our hospital had the florid symptoms and signs pertaining to nervous system without much difficulty in diagnosis. Lack awareness of this life threatning illness is another cause for lack of early diagnosis and late referral [45]. Patients are referred here after occurrence of altered sensorium , focal defecits , seizures and visual impairment .

All patients diagnosed to have tuberculoma presented with seizures. Seizures was more common in tuberculoma than the other form of neurotuberculosis spectrum.On detail enquiry about the seimiology of the seizures the predominant seizure type was focal seizures, followed by focal with secondary generalisations. Maduranth has reported seizures to be the predominant manifestation in patients with tuberculoma [15] . Arseni et al [43]

has reported seizures in 85 % of patients with tuberculoma . Gulati et al [44] have reported that the commest cause of focal seizure was tuberculoma.

Regarding the history of past occurrence of pulmonary tuberculosis none of our patients had pulmonary tuberculosis .A prior history of tuberculosis is present in approximately 10% of adult patients with tuberculous meningitis .[12,13,14]

Michael swash et al[41] have reported a past history of tuberculosis in about 50 % of our patients . This must be due to our rigid inclusion criteria which included only new cases of tuberculosis. Focal deficits were in the form of hemiparesis, hemiplegia, and cranial nerve palsies .

Our study reports vision impairment in 14% of the entire spectrum of neurotuberculosis .The range of vision impairment ranges from legal blindness to functional impairment of vision.None of them at presentation had vol;untered this problem. Sinha*et al*[46] reported that 27% of TBM patients had decreased vision due to optochiasmatic arachanoidtis (OCA). Aaron *et al.*[47] report a figure of 14% with OCA . In view of occurrence of this problem in significant portion of the patients , it has to be anticipated though this problem is not volunteered. Choreothetoid movements were the intial presentation of tuberculoma in 5% of patients. Alarcon et al has also

documented choreoathetoid movement to be the presenting manifestation of tuberculoma[49] .

Spectrum of Neurotuberculosis

The spectrum of neurotuberculosis includes TBM (with or without tuberculoma and spinal arachanoiditis) and isolated tuberculoma. In our study 65 % of the spectrum comprises of TBM (with or without associated tuberculoma). Two studies have documented 70 to 80% of cases of neuro tuberculosis spectrum to be TBM (with or without tuberculoma/ arachanoiditis)[56] .

Staging of the illness:

Clinical staging of the illness as per MRC grading done showed that majority of our patients were in stage 2 (35%) and 3(43 %) of illness at presentation. In tuberculous meningitis the only and single most important physician governed factor irrespective of the treatment regimen which decides about the outcome of the illness is the clinical stage of the illness. Zahra Ahmadinejad hs documented 14.6% in stage I ,34.4% in stage II and 51% in stage III TBM [50] . They found that age, and the clinical stage of the illness [5] were prognostic factors which decided the outcome

Investigatons:

CSF analysis

CSF Protein estimation at presentation in patients with TBM (with or without tuberculoma / archanoiditis) reveled elevated proteins. The levels being 33% had mild elevation (<100 mg/dl), 38% had moderate elevation (101 – 500) and

28 % had severe elevation (> 501) . Eighty eight percentage of patients who presented in stage 2 and stage 3 of illness had moderate to severe elevation of proteins . Ths shows that those who presented in advanced stages had higher levels of CSF proteins [52] [53]. CSF sugars were normal in 55% and reduced less than 2/3^{rds} in 45% 0f patients .There was no correlation between the severity of the illness and the CSF sugar levels.In contrary Hosoglo has found a correlation between severity of the illness and CSF sugar levels[52] . Seventy six percent of the patients showed tuberculous range of lymphocytic pleocytosis . In our study we were not able to document the microorganism in the biologicl fluid. Definitive diagnosis of tuberculous meningitis depends upon the detection of the tubercle bacilli in the CSF, either by smear examination or by bacterial culture. It has been claimed that if large volumes of CSF are carefully examined the organism can be found in over 90% of centrifuged CSF specimens[53] . Bacteriological

diagnosis was made in 107 of 132 adults with clinically suspected tuberulous meningitis[53].

IMAGING

Our study revealed the most common finding on imaging in patients with TBM (with or without tuberculoma/ archnoiditis) to be meningeal enhancement (75%), hydrocephalus (52%), basal exudates (42%) and infarcts (7%) and granulomas (35%). Two studies have revealed basal enhancement of the meninges (particularly in the perimesencephalic cisterns), hydrocephalus, infarction edema often located periventricularly, and mass lesions due to associated tuberculoma or tuberculous abscess, to be imaging abnormlties in descending order[2627]. A study revealed that hydrocephalus was the single most common abnormality seen by CT scan in 52 % to 80% of patients with tuberculous meningitis . Goyal et al studies revealed enhancement of the meninges is seen in approximately 60% of patients with tuberculous meningitis which may be localized or diffuse [31] . Two large community based studies analysed the imaging findings in patients with TBM and found that Hydrocephalus was found in 78% , basal enhancement was found in 38% infarcts in 15-30% and tuberculomas in 5-10% of the patients.

The common site of location of these tuberculomas are parietal and frontal lobe . Multple tuberculoms re more common than solitary tuberculoma. . Infratentorial location of tuberculomas are less frequent . . In

our study we have documented a single case of brain stem tuberculoma in adolescent girl who presented with choreoathetotic movements . The distinctive MRI features of non-caseating granulomas, caseating granulomas with solid or liquid centre was made out [36]. . In our study 14% reported visual impairment but 20% had evidence of enhancement in the optochiasmatic region.

Surgical Intervention

In our study only 6 out of 60 patients required surgical intervention. The procedures done on these patients were ventriculoperitoneal shunt and drainage of the abcess. VP shunt was done in patients with TBM and hydrocephalus. Patients with TBM and hydrocephalus was staged from 1 – 4 [54]. Of the 5 patients who underwent the shunting procedure 2 patients were in stage 2 of illness and 3 were in stage 3 of the illness. The outcome of the procedure was that patients who underwent the shunting procedure in stage 3 illness succumbed to lot of complications like shunt dysfunction , shunt infection requiring shunt revision . Regarding outcome of the patients treated with surgical intervention out of 6 patients 2 died Four patients were labeled as treatment failure , as they continued to develop worsening of clinical features apart from shunt related complications.

The South African study group Lamprect et al had suggested that surgery be reserved for those patients in stage 2 and 3 with obstructive

hydrocephalus rather than those with communicating hydrocephalus.Medical management with mannitol , acetazolamide was adviced for patients in stage 2 with communicating hydrocephalus. Bagavathi et al [48] has reported mortality in 3 out of 7 patients undergoing the shunt procedure. Only 4 out of 9 payients treated by Upthaya et[49] improved following surgery and the rest died at different times following surgery. The mortality rate of those who underwent surgery was 10.7 to 57 % in those with altered sensorium and only 12.5 % in those with normal sensorium.

Outcome

Seventy five percent of those treated with RNTCP regimen were rendered asymptomatic after completion of treatment . Treatment failure was 8.33% and death rate was 3.33 percent . In 16.66% we lost follow up as patients did not turn up for their monthly follow up.

The goal of RNTCP [57] is to achieve a cure rate of 85% in newly diagnosed sputum positive pulmonary tuberculosis and to improve the case detection rate to 70% after the first said goal is achieved . RNTCP focuses mainly on pulmonary tuberculosis and the same targets are maintained for extra pulmonary tuberculosis To document a cure , we need to document the presence of microorganism in the biological fluid and also its clearance after completion of treatment. We were not able to document the microorganism in any of our cases . Diagnosis was done based on a prevalidated criteria and we

were able to see clinical and radiological improvement after treatment which is defined as treatment completed or successful treatment . Though we were not able to document a cure of 85 percent, we were able to demonstrate a successful treatment in 75% of the patients which is close to the target.

In a study from Kerala (n=32) done by Venugopal*et al*[52] who registered 32 cases of neuro tuberculosis under DOTS regimen in their study, of whom 29 completed treatment and all were asymptomatic at the end of treatment (85%). All patients in their study were given 9 months intermittent regimen as per RNTCP guidelines. Five patients (14%) died during treatment. Their result showed that intermittent short course chemotherapy under field program conditions was efficient in curing neuro tuberculosis . DOTS to be effective in TBM (83%). Inspite of choosing cases carefully with a predefined validated criteria for diagnosis and meticulously following up, the the target fixed by the RNTCP could not be achieved . Studies published from India [59 60 61] documents mortality up to 75% and sequelae up to 85%. In our study mortality of 3.33 percent has been documented . The difference in the relative success of treatment of TBM when compared to tuberculoma reflects that the basic immune mediated pathogenetic mechanism play a role in occurrence of new lesions and enlargement of the existing lesions rather than persistence of the infective organism .

CONCLUSION

1) The spectrum of illness of neurotuberculosis affects younger individuals in the age group of 20 to 29 and has a male preponderance.

2) The most common type of presentation of neurotuberculosis is tuberculous meningitis and the common symptom is fever and head ache. The most common manifestation of tuberculoma is seizures.

3) TBM patients present in the advanced stage (stage 2 and stage 3) of the illness.

4) The most common complication of TBM is hydrocephalus and the most devastating complication of neurotuberculosis is visual impairment due to optochiasmatic arachanoiditis .

5) CSF proteins correlated with clinical severity of illness and it can used to prognosticate the adverse outcome.

6) Twenty two percentage of those who had hydrocephalus underwent surgical intervention like ventriculoperitonel shunting . The outcome of surgical intervention is disappointing with deaths occurring in one third, treatment failure in one third , and one third left back with severe neurological sequlae.

7) The outcome of mangement with the standard RNTCP DOTS regimen was that a success rate (treatment completed) of 75%, default rate of 6.6%, mortality rate of 3.3% was obtained . The target fixed by the RNTCP is to achieve a cure rate of 85%.We were able to document a successful completion of treatment in 75% which is close to the target fixed by RNTCP. The default rate is 6.6% which quite negligible when compared to the unsupervised therapy which has a default rate of 50%.

8) Early diagnosis of neurological TB is important because, the timing of initiation of antituberculosis treatment is the most important variable for predicting the outcome in these patients .A high index of clinical suspicion coupled with a battery of imaging and CSF laboratory investigations are required to confirm the diagnosis as it is exceptionally difficult to ascertain histopathological / microbiological proof.

BIBLIOGRAPHY

1. CDC, reported tuberculosis in the United States, 2004. Atlanta, GA. US Department of Health and Human Services, CDC. September 2005.

2. Wood M, Anderson M. Chronic meningitis. In: Neurological infections; major problems in Neurology, vol 16. Philadelphia: WB Saunders, 1998; pp 169–248.

3. Central TB Division. Directorate General Of Health Services. Ministry of Health and Family Welfare. Government Of India. TB India 2010. RNTCP status report. New Delhi: Central TB Division. Directorate General of Health Services.Ministry of Health and Family Welfare; 2010.

4. Mathuranath PS, Radhakrishnan K: Neurological tuberculosis. In: Sharma SK, Mohan A, editors. Tuberculosis, 2nd ed. Jaypee Brothers Medical Publishers (P)Ltd; 2009.P. 304-29.

5. Tandon PN, Bhatia R, Bhargava S. Tuberculous meningitis.In: Harris AA, editor. Handbook of clinical neurology (revised series). Amsterdam: Elsevier Science; 1988.p.l95-226.

6. Donald PR. The epidemiology of tuberculosis in South Africa. Novartis Found Symp 1998;217:24-35; discussion 35-41.

7. Rich AR, McCordock HA. Pathogenesis of tuberculous meningitis. Bull John Hopkins Hosp 1933;52:5-37.

8. Sheller JR, Des Prez RM. CNS tuberculosis. NeurolClin 1986;4:143-58.

9. Bhargava.S, Gupta AK, Tandon PN. Tuberculous meningitis: a CT scan study. Br J Radiol 1982;55:189- 196

10. Hsieh FY, Chia LG, Shen WC. Locations of cerebral infarctions in tuberculous meningitis. Neuroradiology 1992;34:197-9.

11. Tandon PN.Tuberculous meningitis (cranial and spinal). In: Vinken PJ, Bruyn GW, editors. Handbook of clinical neurology. Amsterdam: Elsevier, 1978.

12. Dube MP, Holtom PD, Larsen RA. Tuberculous meningitis in patients with and without human immunodeficiency virus infection. Am J Med 1992;93:520-4.

13. Donald PR, Schoeman JF, Van Zyl LE, De Villiers JN, Pretorius M, Springer P. Intensive short course chemotherapy in the management of tuberculous meningitis. Int J Tuberc Lung Dis 1998;2:704-11.

14. Auerbach O. Tuberculous meningitis: correlation of therapeutic results with the pathogenesis and pathologic changes. I. General considerations and pathogenesis. Am Rev Tuberc 1951;64:408-18.

15. Mathuranath PS, Radhakrishnan K: Neurological tuberculosis. In: Sharma SK, Mohan A, editors. Tuberculosis, 2nd ed. Jaypee Brothers Medical Publishers (P)Ltd; 2009.P. 304-29.

16. Sutlas PN, Unal A, Forta H, Senol S, Kirbas D. Tuberculous meningitis in adults: review of 61 cases. Infection 2003;31(6):387-91.

17. Karstaedt AS, Valtchanova S, Barriere R, Crewe-Brown HH. Tuberculous meningitis in South African urban adults. QJM 1998;91:743-7.

18. Ogawa SK, Smith MA, Brennessel DJ, Lowy FD. Tuberculous meningitis in an urban medical center. Medicine 1987;66:317-26.

19. Leiguarda R, Berthier M, Starkstein S, Nogues M, Lylyk P.Ischemic infarction in 25 children with tuberculous meningitis. Stroke 1988; 19:200-4.

20. Traub B, Colchester AE, Kingsley DP, Swash M. Tuberculosis of the central nervous system. QJM 1984;3:81-100.

21. Kox LF, Kuijper S, KolkAH.Early diagnosis of tuberculous meningitis by polymerase chain reaction. Neurology 1995;45:2228-32.

22. Donald PR, Victor TC, Jordaan AM, Schoeman JF, van Helden PD. Polymerase chain reaction in the diagnosis of tuberculous meningitis. Scand J Infect Dis 1993;25:613-7.

23. Narita M, Matsuzono Y, Shibata M, Togashi T. Nested amplification protocol for the detection of Mycobacterium tuberculosis. ActaPediatr 1992;81:997-1001.

24. Lee BW, Tan JA, Wong SC, et al. DNA amplification by the polymerase chain reaction for the rapid diagnosis of tuberculous meningitis. Comparison of protocols involving three mycobacterial DNA sequences, IS6110, 65 kDa antigen, and MPB64. J NeurolSci 1994;123:173-9.

25. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) an. Am J RespirCrit Care Med. Apr 2000;161(4 Pt 2):S221-47

26. Bullock MR, Welchman JM. Diagnostic and prognostic features of tuberculous meningitis on CT scanning. J NeurolNeurosurg Psychiatry 1982;45:1098-101.

27. Whiteman ML. Neuroimaging of central nervous system tuberculosis in HIV-infected patients. Neuroimaging Clin N Am 1997;7:199-214.28

28. Waecker NJ Jr, Connor JD. Central nervous system tuberculosis in children: a review of 30 cases. Pediatr Infect Dis J 1990;9:539

29. Offenbacher H, Fazekas F, Schmidt R, et al. MRI in tuberculous meningo encephalitis: report of four cases and review of the neuro imaging literature. J Neurol 1991;238:340-4.

30. Bhargava S, Gupta AK, Tandon PN. Tuberculous meningitis--a CT study. Br J Radiol 1982;55:189-96. 31

31. Goyal M, Sharma MC, Gaikwad SB, Mishra NK, Sharma A. Imaging appearance of pachymeningeal tuberculosis. AJR Am J Roentgenol 1997;169:1421-4.

32. Parney IF, Allen PB, Johnson ES. "Idiopathic" cranial hypertrophic pachymeningitis responsive to antituberculous therapy. Neurosurgery 1997;41:965-71.

33. Andronikou S, Smith B, Hatherhill M, Douis H, Wilmshurst J. Definitive neuroradiological diagnostic features of tuberculous meningitis in children. PediatrRadiol 2004;34:876-85.

34. Van Dyk A. CT of intracranial tuberculomas with special reference to the “target sign”.Neuroradiology 1988;30:329

35. Rajshekhar V, Haran RP, Prakash SG, Chandy MJ. Differentiating solitary small cystiorcus granulomas and tuberculomas in patients with epilepsy: clinical and computed tomographic criteria. J Neurosurg 1993;78:402–7.

36. Jinkins JR, Gupta R, Chang KH, Rodriguez- Carbajal J. MR imaging of central nervous system tuberculosis. RadiolClin North Am 1995; 33:771–86.

37. Ahuja GK, Mohan KK, Prasad K, Behari M. Diagnostic criteria for tuberculous meningitis and their validation.Tuber Lung Dis 1994;75:149-52.

38. Schoeman JF, Vanzyl LF, Laubscher JA, Donald PR. Effect of cortico-steroids on intracranial pressure, computed tomographic findings, and

clinical outcome in young children with tuberculous meningitis. Pediatrics 1997;99:226–31.

39. Kumarvelu S, Prasad K, Khosla A, BehariM, Ahuja GK. Randomized controlled trial of dexamethasone intuberculous meningitis. Tubercle Lung Dis 1994;75:203–7.

40. Kaojarern S, Supmonchai K, PhuapraditP,Mokkhavesa C, Krittiyanunt S. Effects ofsteroids on cerebrospinal fluid penetration of antituberculous drugs in tuberculous meningitis. ClinPharmacol Ther1991;49:6–12.

41. Michael swash, John Oxbury. Clinical Neurology, Churchill Livingston. 1991.

42. De Angeles L. Intracranial Tuberculoma – A case report and review of literature.

43. Arsen. C 201 cases of intra cranial tuberculoma treated surgically – Journal of neurology and psychiatry. 1958, 21 308 – 311.

44. Gulti P. Jenu . Tripthi , R.P. and Gupta A.K. MRI in childhood epilepsy – Indian Paediatrics 1991, 28, 761

45. Mehta D, Bassi R, Singh M, Mehta C. To study the knowledge about tuberculosis management and national tuberculosis program among medical students and aspiring doctors in a high tubercular endemic country. Ann Trop Med Public Health 2012;5:206-8

46. Sinha MK, Garg RK, Anuradha HK, Agarwal A, Singh MK, Verma R, et al. Vision impairment in tuberculous meningitis: Predictors and prognosis. J NeurolSci 2010;290:27-32.

47. Aaron S, Alexander M, Mathew V, Anupriya A, Sunithi M, Maya T,et al.Tuberculous optochiasmatic arachnoiditis. Neurol India 2010; 58:732-5.

48. Thwaites GE, Hien TT. (2005B) Tuberculous meningitis: many questions, too few answers. Lancet neurol 4:160 -170.

49. Alrcon F Ducnas G Cevallos N , Lees AJ. Movement disorders in 30 patients with tuberculous meningitis . Mov. Disorder 2000 ; 15:561- 9

50. The Internet Journal of Infectious Diseases ISSN: 1528-8366 The Prognostic Factors Of Tuberculous Meningitis Zahra Ahmadinejad MD Infectious Diseases Specialist, Assistant Professor , Department of Infectious Diseases, Faculty of Medicine, Tehran University Of Medical Sciences Teheran Iran

51. Lu CH. Chang WN. Chang HW. The prognostic factors of adult tuberculous meningitis. Infection, 2001; 29(6): 299-304.

52. Hosoglo S, Ayaz C, Geyik MF, et al. Tuberculous meningitis in adults: an eleven-year review. Int J Tuberc Lung Dis., 1998; 2(7):553-7.

53. Molavi A, LeFrock JL. Tuberculous meningitis. Med Clin North Am 1985;69:315–31.

54. Palur R, Rajashekhar V, ChandyMJ, Joseph T , Abraham J . Shunt surgery for hydrocephalus in tubercular meningitis. A long term follow up

55. Fallon RJ, Kennedy DH. Treatment and prognosis in tuberculous meningitis. JInfect 1981;3:39-44. 56

56. Wang JT, Hung CC, Sheng WH, Wang JY, Chang SC, Luh KT. Prognosis of tuberculous meningitis in adults in the era of modern antituberculous chemotherapy. J Microbiol Immunol Infect 2002;35:215-22.

57. Ramachandran P, Duraipandian M, Nagarajan M, Prabhakar R, Ramakrishnan CV, Tripathy SP. Three chemotherapy studies of tuberculous meningitis in children. Tubercle 1986;67:17-29.

PROFORMA

1. Name : Age / Sex :
2. OP / IP :
3. Address :
4. Clinical Features : Signs & Symptoms
   - Headache
   - Fever
   - Vomiting
   - Seizures
   - Focal Deficit
   - Pappiledema
   - Visual Impairment
   - Meningeal Signs

5. Clinical Staging of Illness (MRC)
   - Stage I :
   - Stage II :
   - Stage III :

6. Investigations
   - CBC
   - RFT
   - LFT
   - Chest X-Ray
   - HIV
   - CT / MRI (Brain)

- CSF
    - Cells
    - Proteins
    - Gram Stain
    - AFB Stain
    - Fungal Stain

8. Treatment

- Medical – ATT Category 1

Duration of Months
9 Months
10 Months
12 Months

- Surgical

9. Followup : Assessment

- Clinical
- Biochemical
- Radiological

10. Outcome

- Treatment Successful
- Failure
- Defaulter
- Death
- Lost follow up

MASTER CHART

NAME	AGE/SEX	DIAGNOSIS	STAGE	SYMPTOMS & SIGNS							IMAGING		CSF ANALYSIS				ATT DURATION	SURGERY	OUTCOME
				FEVER	HEAD ACHE	ALT.SENSORIUM	SEIZURES	DEFICIT	MENINGEAL SIGNS	VISION	CT BRAIN	MRI brain	CSF cells	PROTEINS mg/dl	SUGAR mg/dl	AFB			
SUDHAKAR	17/M	TBM/TUBER	I	NO	YES	No	GTCS	No	Yes	NORMAL	Normal	ME	Few lymph.	78	54	Nil	9	Nil	SUCCESS
MD. KHAN	22/m	TUBERCULOMA	-	NO	YES	NO	FOCAL	NO	NO	NORMAL	hypodense	B E	NIL	NIL	NIL	NIL	9	NIL	SUCCESS
ANITHA	27/F	TBM/TUBERCULOMA	I	NO	YES	NO	FOCAL	NO	NO	NORMAL	NORMAL	B E	NIL	125	24	NIL	12	NIL	SUCCESS
SUKUMAR	24/M	TBM/TUBERCULOMA	II	YES	YES	YES	GTCS	NO	NO	NORMAL	ME	ME	12 LYMPH	43	45	NIL	9	NIL	SUCCESS
KUTTIAMMA	35/ F	TBM/TUBERCULOMA	III	YES	YES	YES	GTCS	YES	YES	VI	ME	BE/HY	46 LYMPH	480	56	NIL	9	NIL	SUCCESS
KANNAN	48/M	TBM	III	YES	YES	YES	FOCAL	YES	YES	NORMAL	NORMAL	HY	23 LYMPH	120	23	NIL	12	VPSHUNT	FAILURE
PARVATHY	32/f	TBM	III	YES	YES	YES	GTCS	YES	YES	VI	I/BE/HY	E/I/H	56 LYMPH	1.2	12	NIL	3	VP SHUNT	DEATH
KATHARINA	21/M	TBM	I	YES	YES	YES	GTCS	YES	YES	NORMAL	NORMAL	ME/HY	NIL	54	43	NIL	9	NIL	SUCCESS
SUDALAI	22/m	TBM/TUBE	II	YES	YES	YES	NO	NO	YES	NORML	H/ME	H/ME	48 L	76	32	NIL	9	NIL	SUCCESS
AYUBKHAN	19/m	TBM	III	YES	YES	YES	GTCS	YES	YES	NORMAL	H/ME	H/ME	12 LYMPH	65	34	NIL	9	NIL	SUCCESS
RUDRAKUMAR	25/M	TBM	III	YES	YES	YES	GTCS	YES	YES	NORMAL	H	ME/H	18 L	100	23	NIL	10	nil	success
BAKIYAVATHY	37/f	spinal aracha -	III	NO	no	no	YES	YES	YES	NORMAL	ara	arac	76L	65	24	NIL	9	NIL	SUCCESS
KARTHICK	21/m	TBM	III	YES	YES	YES	NO	YES	YES	ME	ME	be/hy	67L	300	23	NIL	12	NIL	LOST FOLLOW
LAKSHMI	25/F	TBM	III	YES	YES	YES	GTCS	YES	YES	IMPAIRDE H/I/ENHA		ME/H	87L	1.5GMS	34	NIL	4	VPSHUNT	DEATH
SURESH	31/M	TBM	II	YES	YES	YES	FOCAL	YES	YES	H	NORMAL	H OBS.	76L	150	12	NIL	12	VPSHUNT	FAILURE
RAVEENDRA	30/M	TUBERCULOMA	I	NO	no	NO	FOCAL	NO	NORMAL	NORMAL	G	FG	NIL	NIL	NIL	NIL	9	NIL	SUCCESS
PREMA NATAR	50/F	TBM/TUBE	II	NO	YES	NO	FOCAL	NO	NORMAL	NORMAL	FP TUBER	G	23L	450	23	NIL	12	NIL	SUCCESS
SUKUMAR	24/m	TBM	III	YES	YES	YES	GTCS	YES	YES	IMPAIRED	OCA	BE/OCA/H	78L	600	14	NIL	9	NIL	SUCCESS
AJITHA	51/f	F TUBER	-	NO	NO	NO	FOCAL	NO	NORMAL	NORMAL	F TUBER	FT	NIL	NIL	NIL	NIL	9	NIL	SUCCESS
GOVINDHAN	15/m	TBM	II	YES	YES	YES	NO	YES	YES	NORML	ME	ME	21 L	67	32	NIL	9	NIL	SUCCESS
VEERAMMA	20/f	TBM/TUBER	II	YES	YES	YES	FOCAL	NO	YES	NORMAL	NORML	ME/G	34 L	87	32	NIL	10	NIL	SUCCESS
SARITHA	29/f	TBM/TUBER	II	YES	YES	NO	GTCS	YES	YES	NORMAL	NORMAL	ME	23 L	94	23	NIL	9	NIL	SUCCESS
AYYANAR	28/m	p tuber	-	YES	yes	NO	FOCAL	YES	NORMAL	NORMAL	NORMAL	PG	NIL	NIL	NIL	NIL	12	NIL	DEFAULT
BANU	14/f	TBM	II	YES	YES	YES	YES	YES	YES	NORMAL	NORMAL	ME	FEW	87	34	NIL	9	NIL	SUCCESS
CHOKKU	33/m	TBM/TUBER	II	YES	YES	YES	FOCAL	YES	YES	VI	ME	ME	23 L	87	32	NIL	10	NIL	SUCCESS
RAVI	28/m	TBM	II	YES	YES	YES	NO	YES	YES	NORMAL	BE	normal	23 L	98	21	NIL	12	NIL	SUCCESS
RANI	24/f	f tuber	-	YES	yes	NO	FOCAL	YES	NORMAL	NORMAL	FG	FG	NIL	NIL	NIL	NIL	12	NIL	SUCCESS
CHINNAPPA	38/m	TBM	II	YES	YES	YES	NO	YES	YES	NORML	NORML	BE	FEW CELLS	65	32	NIL	12	NIL	SUCCESS
ELANGO	24/m	s arahano	III	YES	YES	No	YES	YES	NORMAL	NORMAL	VI	arac	56	43	26	NIL	10	NIL	DEFAULT
SUBBSMA	39/f	TBM	III	YES	YES	YES	YES	YES	YES	IMPAIR	OCA	oca/be	28 L	643	11	NIL	9	NIL	SUCCESS

MASTER CHART

NAME	AGE/SEX	DIAGNOSIS	STAGE	SYMPTOMS & SIGNS							IMAGING		CSF ANALYSIS				ATT DURATION	SURGERY	OUTCOME
				FEVER	HEAD ACHE	ALT.SENSORIUM	SEIZURES	DEFICIT	MENINGEAL SIGNS	VISION	CT BRAIN	MRI brain	CSF cells	PROTEINS mg/dl	SUGAR mg/dl	AFB			
FARIQ	27/M	TBM	III	YES	YES	YES	NO	YES	YES	IMPAIR	OCA	oca/be/	23 L	345	23	NIL	12	VPSHUNT	SUCCESS
THARANI	28/f	fp tuber		YES	no	NO	FOCAL	YES	NORMAL	NORMAL		f g	NIL	NIL	NIL	NIL	9	NIL	LOST FOLLOW
RAJU	46/m	TBM	I	YES	YES	NO	NO	NO	YES	NORMAL		normal	23 L	52	NIL	NIL	10	NIL	SUCCESS
RAVI	19/m	TBM	III	YES	YES	YES	YES	YES	YES				56 L	230	12	NIL	9	NIL	DEFAULT
KANNAGI	25/f	TBM	III	YES	YES	YES	YES	YES	YES	IMPAIRE	OCA	oca/i/hydr	32 L	176	32	NIL	10	VPSHUNT	SUCCESS
SHANKAR	47/m	PF TUBER		NO	yes	NO	FOCAL	YES	NORMAL	NORMAL		pf g	NIL	N	NIL	NIL	9	NIL	FAILURE
THIRUMAL	42/m	TBM	I	YES	YES	NO	NO	NO	YES	NORMAL		normal	FEW CE	53	32	NIL	10	NIL	SUCCESS
SATISH	25/m	TUBERCUL		YES	no	NO	GTCS	YES	NORMAL	NORMAL		f g	NIL	NIL	NIL	NIL	9	NIL	LOST FOLLOW
KRISHANA	46/m	TBM	I	YES	YES	NO	NO	NO	YES	NORMAL		normal	10 L	49	NIL	NIL	10	NIL	SUCCESS
PAUL	23/m	TUBERCUL		NO	yes	NO	FOCAL	YES	NORMAL	NORMAL	FG	FG	NIL	N	NIL	NIL	9	NIL	SUCCESS
MANGAMA	28/f	TBM/TUB	I	YES	YES	NO	FOCAL	NO	YES	NORMAL	G	G	18 L	49	21	NIL	10	NIL	SUCCESS
JOE	28/m	TUBERCUL		YES	no	NO	FOCAL	YES	NORMAL	NORMAL	G	G	NIL	N	NIL	NIL	9	NIL	LOSTFOLLOW
RAJA	47/m	TBM	I	YES	YES	NO	NO	NO	YES	NORMAL	NORMAL	normal	13 L	51	21	NIL	10	NIL	SUCCESS
HELEN	41/f	TBM/TUB	III	YES	YES	YES	NO	YES	YES	VI	H	I/E/H	34 L	180	12	NIL	9	NIL	SUCCESS
PREMA NATAR	50/F	TUBERCUL		YES	yes	NO	FOCAL	YES	NORMAL	NORMAL	FG	FG	NIL	N	NIL	NIL	10	NIL	SUCCESS
DHARANI	25/f	arachano		NO	NO	YES	NO	YES	NORMAL	NORMAL	ME	sp ara	56L	67	12	Nil	9	NIL	SUCCESS
MURUGAN	18/m	brain stem t		no	no	NO	NO	YES	NO	NORMAL	G	granu	14 L	76	21	NIL	10	NIL	SUCCESS
RAJI	47/m	TBM	III	YES	YES	YES	NO	YES	YES	VI	H	ME/H	32L	198	12	NIL	9	NIL	SUCCESS
SUNDAR	28/m	TBM/TUB	II	YES	YES	NO	NO	NO	YES	VI	H	ME/BE/H	43 L	98	21	NIL	10	NIL	SUCCESS
KATHIR	48/m	P TUBERCULOMA		YES	yes	NO	FOCAL	YES	NORMAL	NORMAL	PG	PG	NIL	NIL	NIL	NIL	10	NIL	SUCCESS
ANTONY	52/m	TBM	II	YES	YES	YES	NO	YES	YES		H	ME/H	12 L	98	21	NIL	9	NIL	SUCCESS
PANDI	23/m	FPTUBERCULOMA		NO	yes	NO	FOCAL	YES	NORMAL	NORMAL	FG	FG	NIL	NIL	NIL	NIL	10	NIL	SUCCESS
PONNI	53/f	TBM/TUBE	III	YES	YES	YES	NO	YES	NO	VI	H	ME/BE/H	60 L	309	14	NIL	9	NIL	LOST FOLLOW
MANIMAL	18/f	TUBERCULOMA		NO	no	NO	GTCS	YES	NORMAL	NORMAL	G	G	NIL	NIL	NIL	NIL	10	NIL	SUCCESS
MUNISAMI	53/m	TBM/TUB	II	YES	YES	YES	FOCAL	NO	NO	NORMAL	H	HYDRO	10 L	65	12	NIL	10	NIL	SUCCESS
PANCHALAI	52/f	TUBERCULOMA		NO	no	NO	FOCAL	YES	NORMAL	NORMAL	FG	FG	NIL	NIL	NIL	NIL	9	NIL	DEFAULT
VENKATAMA	26/f	TBM	II	YES	YES	YES	NO	YES	YES	NORMAL	H	HYDRO	34 L	98	14	NIL	10	NIL	SUCCESS
PAZANI	18/m	TUBERCULO	III	YES	no	YES	GTCS	YES	NORMAL	NORMAL	H	ME/H	34 L	123	15	NIL	9	NIL	LOST FOLLOW
MEGALA	27/m	TBM/TUBE	III	YES	YES	YES	NO	YES	NO	NORML	H	H	34 L	243	19	NIL	10	NIL	SUCCESS
NISHA	19/f	TUBERCULOMA		NO	no	NO	GTCS	YES	NORMAL	NORMAL	FG	FG	NIL	NIL	NIL	NIL	9	NIL	SUCCESS

KEY FOR MASTER CHART

ME	-	Meningeal Enhancement
BE	-	Basal Exudates
H	-	Hydrocephalus
L	-	Lymphocytes
G	-	Granuloma
P	-	Parietal
F	-	Frontal
VI	-	Visually Impaired

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE. CHENNAI -3

Telephone No : 04425305301
Fax : 04425363970

CERTIFICATE OF APPROVAL

To
Dr. E. Uma Maheswari
PG in DM Neurology
Madras Medical College, Chennai -3

Dear Dr. E. Uma Maheswari

The Institutional Ethics Committee of Madras Medical College reviewed and discussed Your application for approval of the proposal entitled "Clinical spectrum of neurotuberculosis And Analysis of outcome of RNTCP treatment regimens in various forms of neurological tuberculosis
No. 39092011

The following members of Ethics Committee were present in the meeting held on 27.09.2011 conducted at Madras Medical College, Chennai -3

1.	Dr. S.K. Rajan MD	-- Chairperson
2.	Dr. V. Kanagasabai MD Dean, Madras Medical College, Chennai -3	-- Deputy Chairman
3.	Prof. R. Sundaram MD Vice Principal, Madras Medical College, Chennai -3	--Member Secretary
4.	Prof. R. Nandhini MD Director, Inst. Of Pharmacology, M M C, Ch -3	-- Member
5.	Prof. Pregna B. Dolia MD Director , Inst. of Biochemistry, M M C, Ch -3	-- Member
6.	Thiru . Ulaganathan Administrative Officer, M M C, Ch -3	-- layperson
7.	Thiru. S. Govindasamy BA BL	-- Lawyer
8.	Tmt. Arnold saulina .MA., MSW	-- Social Scientist

We approve the Proposal to be conducted in this presented from

Sd/ Chairman & Other Members

The institutional Ethics Committee expects to be informed about the progress of the study, Any SAE occurring in the course of the study , any change in the protocol and patient information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics committee

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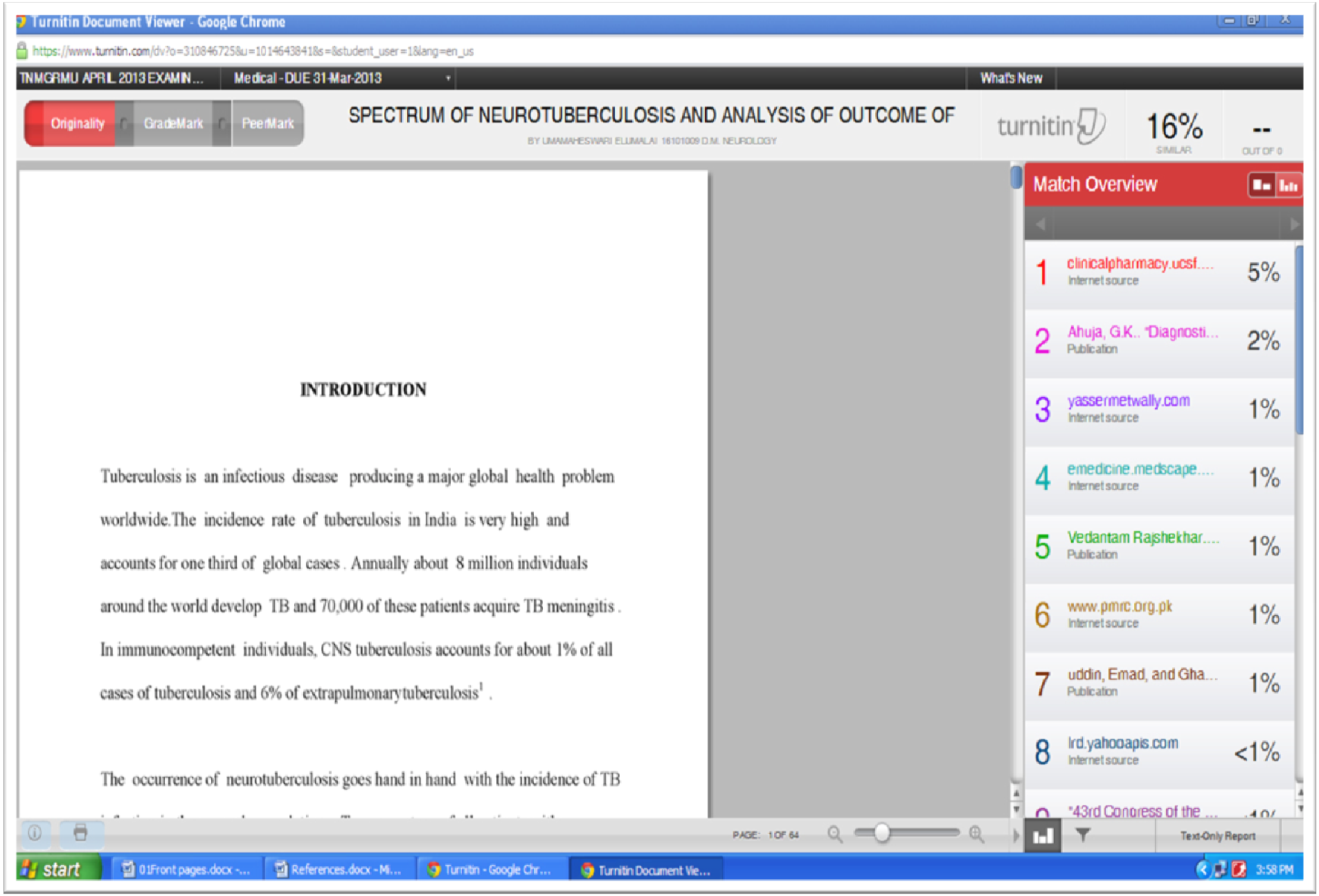
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